PROCEEDINGS

OF THE

NEW YORK PATHOLOGICAL SOCIETY

NEW SERIES, VOLUME XV

1915

ORGANIZED IN 1844

INCORPORATED IN 1886

NEW YORK
1915

PRESS OF
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LIST OF OFFICERS AND COMMITTEES FOR THE YEAR 1915

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DR. F. C. WOOD

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DR. ALWIN PAPPENHEIMER
DR. F. C. WOOD, *Treasurer*
DR. L. W. FAMULENER, *Secretary and Editor*

Committee on Microscopy:
DR. JAMES EWING
DR. CHARLES NORRIS
DR. F. C. WOOD

PRESIDENTS OF THE SOCIETY.

*Dr. John A. Sweet 1844
*Dr. Willard Parker 1845, 1846, 1847
*Dr. James R. Wood 1848, 1857
*Dr. T. M. Markoe 1849, 1879
*Dr. W. H. Van Buren 1850
*Dr. Charles E. Isaacs 1851
*Dr. John T. Metcalfe 1852
*Dr. Henry Van Arsdale 1853
*Dr. James Bolton 1854, 1855
*Dr. Robert Watts 1856
*Dr. Edmund R. Peaslee 1858
*Dr. John C. Dalton 1859
*Dr. Alfred C. Post 1861
*Dr. Thomas C. Finnell 1862
*Dr. David S. Conant 1863
Dr. Abraham Jacobi 1864
*Dr. Gurdon Buck 1865
*Dr. Henry B. Sands 1866
*Dr. William B. Bibbins 1867
*Dr. Ernest K. Krackowitzer 1868
*Dr. L. A. Sayre 1869
*Dr. Joseph C. Hutchinson 1870
*Dr. A. L. Loomis 1871, 1872
*Dr. Erskine Mason 1873
*Dr. Herman Knapp 1874
*Dr. Francis Delafield 1875
Dr. Charles K. Briddon 1876
*Dr. Edward G. Janeway 1877
*Dr. John C. Peters 1878
Dr. Edward L. Keyes 1879
Dr. T. E. Satterthwaite 1880, 1881
*Dr. E. C. Seguin 1882
*Dr. George F. Shrady 1883, 1884
Dr. John A. Wyeth 1885, 1886
Dr. T. M. Prudden 1887, 1898, 1899

* Deceased.

Dr. W. P. Northrup	1888, 1889
*Dr. J. West Roosevelt	1890
Dr. Hermann M. Biggs	1891
*Dr. H. P. Loomis	1892, 1893
*Dr. G. C. Freeborn	1894
Dr. George P. Biggs	1895
*Dr. John Slade Ely	1896, 1897
*Dr. Eugene Hodenpyl	1900
Dr. Edward K. Dunham	1901
Dr. James Ewing	1902
Dr. William H. Park	1903
Dr. O. H. Schultze	1904
Dr. Harlow Brooks	1905
Dr. F. S. Mandlebaum	1906
Dr. Charles Norris	1907
Dr. E. Libman	1908
Dr. Horst Oertel	1909
Dr. Richard M. Pearce	1910
Dr. W. G. MacCallum	1911, 1912
Dr. A. B. Wadsworth	1913
Dr. Alwin M. Pappenheimer	1914
Dr. Hans Zinsser	1915

SECRETARIES.

*Dr. W. C. Roberts	1844 to 1849
*Dr. H. D. Buckley	——
*Dr. Henry G. Cox	1850 to 1852
*Dr. William H. Church	1852
*Dr. Chas. M. Allen	1852 to 1853
*Dr. Geo. T. Elliot	1853 to 1854
*Dr. J. F. Jenkins	1854 to 1855
*Dr. E. Lee Jones	1855 to 1861
*Dr. T. G. Thomas, *pro tem*	1855
*Dr. H. D. Noyes, *pro tem*	1858
*Dr. Geo. F. Shrady	1861 to 1879
*Dr. W. M. Carpenter	1880 to 1888
Dr. Walter Mendelson	1888

* Deceased.

Dr. T. L. Stedman ..... 1889 to 1891
Dr. Ogden C. Ludlow ..... 1891 to 1902
Dr. F. C. Wood ..... 1902 to 1907
Dr. Karl M. Vogel ..... 1907 to 1910
Dr. Alwin M. Pappenheimer ..... 1911 to 1914
Dr. Robert A. Lambert 1914
Dr. L. W. Famulener 1915

LIFE MEMBERS OF THE SOCIETY

Elected		
1877	Abbe, Robert	13 West 50th Street
1889	Carter, De Lancy	118 East 85th Street
1887	Cheesman, Timothy M.	Garrison-on-Hudson, New York
1884	Dixon, George A.	15 West 49th Street
1889	Dunham, Edward K.	35 East 68th Street
1855	Eliot, Ellsworth	34 East 67th Street
1853	Emmet, Thomas Addis	89 Madison Avenue
1888	Freeman, Rowland G.	211 West 57th Street
1874	Gibney, Virgil P.	16 Park Avenue
1889	Grauer, Frank	226 West 71st Street
1887	Hamilton, Charles S.	150 East Broad St., Columbus, Ohio
1882	Holt, L. Emmett	14 West 55th Street
1880	Jackson, Frank W.	555 Madison Avenue
1861	Jacobi, Abraham	19 East 47th Street
1887	James, Walter B.	7 East 70th Street
1879	Judson, A. B.	53 Washington Square
1871	Leale, Charles A.	604 Madison Avenue
1883	LeBoutillier, William G.	Long Lake, Hamilton Co., N. Y.
1880	Lewis, Daniel	616 Madison Avenue
1885	Lockwood, George Roe	18 East 52d Street
1889	MacHale, Ferdinand	317 East 87th Street
1878	McNutt, Sarah J.	265 Lexington Avenue
1878	Mayer, Abraham	40 East 60th Street
1886	Meyer, Willy	700 Madison Avenue
1874	Moeller, Henry	140 West 88th Street
1883	Northrup, William P.	57 East 79th Street
1858	Packard, Charles W.	455 Park Avenue
1886	Peterson, Frederick	20 West 50th Street
1874	Polk, William M.	310 Fifth Avenue

Elected

1878 Porter, William H. .....46 West 83d Street
1883 Prudden, T. Mitchell.....160 West 59th Street
1884 Rice, Clarence C. .....123 East 19th Street
1881 Robinson, A. R. .....159 West 49th Street
1874 Satterlee, F. LeRoy.....6 West 56th Street
1872 Satterthwaite, Thomas E.....7 East 80th Street
1887 Sayre, R. H. .....14 West 48th Street
1890 Seaman, Louis L. .....247 Fifth Avenue
1872 Stimson, Daniel M. .....28 West 37th Street
1886 Thacher, John S. .....20 West 50th Street
1888 Van Cott, J. M. .....188 Henry Street, Brooklyn
1878 Walker, Henry F. .....18 West 55th Street
1882 Wiener, R. G. .....48 East 65th Street
1885 Wright, Jonathan,
Windy Rock, Westchester Co., Pleasantville, N. Y.
1881 Wylie, W. Gill.....28 West 40th Street

MEMBERS OF THE SOCIETY

Elected

1898 Adler, Isaac.....401 West End Avenue
1914 Baehr, George.....51 East 96th Street
1898 Bailey, Frederick R.....1465 N. J. Avenue, Elizabeth, N. J.
1907 Bang, Richard T.....139 West 11th Street
1903 Bartlett, C. J.....183 Bishop Street, New Haven, Conn.
1902 Bastedo, Walter A.....57 West 58th Street
1892 Beach, Bennett S.....144 West 85th Street
1905 Beer, Edwin.....48 West 74th Street
1900 Berkeley, W. N.....133 East 61st Street
1913 Bernstein, Harry S....Health Department, Providence, R. I.
1891 Biggs, George P.....133 West 71st Street
1901 Bishop, Louis F.....54 West 55th Street
1911 Boehm, Emil.....3806 Delmar Boulevard, St. Louis, Mo.
1905 Bolduan, Charles F.....139 Centre Street
1896 Bovaird, David.....137 East 60th Street
1901 Brill, N. E.....48 West 76th Street
1896 Brooks, Harlow.....44 West 9th Street
1908 Buerger, Leo.....40 East 41st Street
1913 Burrows, M. T.,
Johns Hopkins Medical School, Baltimore, Md.

Elected		
1911	Butterfield, E. E.	135 East 34th Street
1915	Cary, Edward G.	1145 Amsterdam Avenue
1910	Cecil, Russell L.	123 East 62d Street
1908	Celler, Herbert L.	61 West 94th Street
1913	Coca, A. F.	342 State Street, Flushing, N. Y.
1909	Cohn, A. E.	316 Central Park West
1910	Cole, Rufus	960 Park Avenue
1891	Coleman, Warren	58 West 55th Street
1893	Coley, William B.	521 Park Avenue
1903	Collins, Katherine R.	State Board of Health, Atlanta, Ga.
1914	Cornwall, Leon H.	375 Park Avenue
1896	Denton, Myron B.	129 East 30th Street
1914	Diner, Jacob	316 West 84th Street
1913	Eisenbrey, A. B.	St. Luke's Hospital
1910	Elsberg, C. A.	Madison Avenue and 63d Street
1901	Elser, William J.	Cornell Med. Col., 1st Ave. and 28th St.
1915	Evans, Frank A.	Presbyterian Hospital
1908	Ewald, Louis A.	48 East 87th Street
1893	Ewing, James	264 West 57th Street
1909	Famulener, L. W.	St. Luke's Hospital
1913	Felberbaum, David	561 West 163d Street
1901	Field, Cyrus W.	24 East 48th Street
1905	Flexner, Simon	Rockefeller Inst., Avenue A and 66th St.
1892	Fordyce, John A.	8 West 77th Street
1912	Fox, Fred J.	124 East 19th Street
1905	Frank, Robert T.	983 Park Avenue
1915	Fraser, Alexander	601 West 148th Street
1914	Fried, G. A.	315 Central Park West
1913	Garside, C. Z.	Hotel Bretton Hall, Bway. and 86th Street
1903	Goodman, A. L.	136 West 87th Street
1914	Gutherson, W. F.	37 Hamilton Street, Paterson, N. J.
1908	Haas, Sidney V.	666 West End Avenue
1911	Hall, Morton E.	11125 89th Ave., Edmonton, Alberta, Can.
1912	Harvey, S. C.	Peter Bent Brigham Hospital, Boston, Mass.
1905	Hastings, Thomas	22 East 68th Street
1907	Hess, Alfred F.	16 West 86th Street
1912	Hillman, Oliver	214 West 110th Street
1915	Holt-Harris, J. E.	Quarantine Station, Rosebank, N. Y.

Elected		
1911	Hopkins, J. G.	350 Washington Ave., Brooklyn
1893	Huddleston, John H.	145 West 78th Street
1911	Huffman, Otto V.	89 Joralemon Street, Brooklyn
1912	Humphreys, Frederick B.	630 West 141st Street
1911	Huntoon, F. M.	Cornell Med. Col., First Ave. and 28th St.
1894	Jeffries, Ferdinand	341 West 50th Street
1900	Jessup, D. S. D.	601 West 113th Street
1913	Jobling, J. W.	Vanderbilt University, Nashville, Tenn.
1903	Jones, S. Fosdick.	250 Metropolitan Building, Denver, Colo.
1909	Kast, Ludwig	771 Madison Avenue
1903	Keller, F. C.	77 West 50th Street
1910	Kessel, Leo	88 Central Park West
1915	Kline, Benjamin S.	Montefiore Hospital, N. Y.
1891	Kneer, Ferdinand G.	236 West 51st Street
1908	Kohn, Albert	122 East 58th Street
1910	Krumwiede, C.	15 Hobart Street, Bronxville, N. Y.
1912	Lamb, Albert	171 East 71st Street
1893	Lambert, Alexander	43 East 72d Street
1912	Lambert, R. A.	735 Park Avenue
1899	Langmann, Gustav	121 West 57th Street
1907	Lapowski, Boleslaw	180 West 58th Street
1896	Larkin, John H.	City Hospital
1904	Leale, Medwin	852 Lexington Avenue
1912	L'Esperance, Elise.	Cornell Med. Col., 1st Ave. and 28th St.
1898	Levin, Isaac	119 West 71st Street
1915	Levy, I. J.	76 West 86th Street
1908	Lewisohn, Richard	565 Park Avenue
1899	Libman, Emanuel	180 East 64th Street
1908	Lindsay, Gordon	1337 71st Street, Brooklyn
1911	Longcope, Warfield T.	116 East 58th Street
1915	Long, W. Bayard	1257 Washington Avenue
1891	McAlpin, D. Hunter	68 William Street
1910	McDonald, Ellice	174 West 58th Street
1900	McLaughlin, George E.	41 Crescent Avenue, Jersey City
1909	MacCallum, W. G.	437 West 59th Street
1912	MacNeal, Ward J.	303 East 20th Street
1905	Mandel, Arthur R.	150 East 40th Street
1895	Mandlebaum, F. S.	1300 Madison Avenue

Elected		
1901	Manges, M.	72 East 79th Street
1900	Mannheimer, George	41 West 51st Street
1899	Markoe, James W.	20 West 50th Street
1909	Martland, H. S.	1138 Broad Street, Newark, N. J.
1901	Meltzer, S. J.	Rockefeller Institute, Avenue A and 66th St.
1898	Moschcowitz, Alexis V.	925 Madison Avenue
1904	Moschcowitz, Eli	41 West 83d Street
1903	Murray, Archibald	36 Gramercy Park
1892	Myles, Robert C.	46 West 38th Street
1894	Norrie, Van Horne	21 West 37th Street
1896	Norris, Charles	Bellevue Hospital
1895	Noyes, William B.	221 West 57th Street
1899	Oertel, Horst	Royal Victoria Hospital, Montreal, Canada
1914	Olcott, G. P., Jr.	772 Park Avenue
1906	Oppenheimer, B. S.	125 West 86th Street
1915	Ottenberg, Reuben	15 West 89th Street
1905	Pappenheimer, A. M.	437 West 59th Street
1893	Park, William H.	315 West 76th Street
1903	Patterson, Henry S.	130 East 62d Street
1909	Pease, Herbert D.	39 West 38th Street
1913	Petersen, William F.	Vanderbilt University, Nashville, Tenn.
1898	Phillips, Carlin	166 West 72d Street
1900	Potter, N. B.	591 Park Avenue
1912	Ray, Edgar T.	824 St. Nicholas Avenue
1914	Riley, E. J.	605 West 181st Street
1915	Riley, Henry A.	437 West 59th Street
1914	Rohdenberg, G. L.	222 West 136th Street
1891	Sachs, B.	116 West 59th Street
1902	Satterlee, G. R.	125 West 58th Street
1900	Schlapp, Max	40 East 41st Street
1897	Schley, W. S.	24 West 45th Street
1915	Schöhl, Otto	Quarantine Station, Rosebank, N. Y.
1897	Schultze, Otto H.	47 East 58th Street
1910	Schwartz, Benjamin	261 7th Street
1903	Schwarz, Herman	50 East 91st Street
1895	Shelby, Edmund P., Jr.	116 West 74th Street
1913	Sittenfield, M. J.	437 West 59th Street
1899	Smith, Ernest E.	50 E. 41st Street
1894	Sondern, Frederic E.	200 West 56th Street

Elected		
1908	Stein, Arthur P.	11 East 68th Street
1898	Stein, Richard	79 East 79th Street
1901	Steinhardt, E. R.	Research Laboratory, East 16th St.
1911	Stillman, Charles K.	Mystic, Conn.
1913	Stillman, E. G.	17 East 72d Street
1911	Strong, L. W.	Woman's Hospital
1912	Symmers, Douglas	Bellevue Medical School
1912	Taylor, Richard	303 East 20th Street
1915	Teague, Oscar	Quarantine Station, Rosebank, N. Y.
1913	Terry, B. T.	King's County Hospital, Brooklyn
1913	Thalhimer, William	86 West 83d Street
1913	Tytler, W. H.	66 Paisley Street, Guelph, Ont.
1905	Van Beuren, Frederick T., Jr.	812 Park Avenue
1912	Vance, Morgan	Bellevue Hospital
1905	Vogel, Karl M.	680 Madison Avenue
1897	Wadsworth, A. B.	State Dept. of Health, Albany, N. Y.
1911	Wallace, Guy H.	Bellevue Hospital
1907	Ward, Wilbur	24 West 50th Street
1905	Warren, Mortimer	24 Gramercy Park
1904	Weil, Richard	970 Park Avenue
1903	Welch, J. E.	138 West 70th Street
1903	Welt-Kakels, Sara	35 East 61st Street
1908	Wiener, Solomon	67 West 89th Street
1907	Wilcox, Herbert B.	159 East 70th Street
1894	Williams, Anna W.	549 Riverside Drive
1901	Wilson, R. J.	549 Riverside Drive
1913	Woglom, William H.	110 Morningside Drive
1891	Wollstein, Martha	1 West 81st Street
1898	Wood, Francis Carter	1145 Amsterdam Avenue
1912	Youland, W. E.	123 State Street, Albany, N. Y.
1905	Zinsser, Hans	437 West 59th Street

CERTIFICATE OF INCORPORATION.

State of New York,
City and County of New York, } *ss.:*

We, the subscribers, who are severally members of the unincorporated society known as the New York Pathological Society, founded in the City of New York in the year one thousand eight hundred and forty-four, namely:—

ALONZO CLARK,
MIDDLETON GOLDSMITH,
JOHN C. PETERS,
LEWIS A. SAYRE,
THOMAS M. MARKOE,
GUSTAVUS A. SABINE,
JOHN C. DALTON,
ABRAHAM JACOBI,
ALFRED L. LOOMIS,
FRANCIS DELAFIELD,
EDWARD G. JANEWAY,
GEORGE F. SHRADY,
WESLEY M. CARPENTER,
JOHN A. WYETH,
WILLARD PARKER,
THOMAS ADDIS EMMET,
T. MITCHELL PRUDDEN,
WILLIAM P. NORTHRUP,
LOUIS WALDSTEIN,
L. EMMETT HOLT,
JOHN H. HINTON,
GEORGE L. PEABODY,
THOS. E. SATTERTHWAITE,

who are severally Doctors of Medicine, and who severally reside in the City, County, and State of New York, and are citizens thereof, except the above-named Middleton Goldsmith, who resides in Rutland, in the State of Vermont, and is a citizen thereof,

Do hereby certify that we desire to form a Corporation under and in pursuance of Chapter 319 of the Laws of 1848, of the State of New York, entitled "An Act for the incorporation of benevolent, charitable, scientific, and missionary societies," and the several acts amending and extending the same; particularly Chapter 526 of the Laws of 1881, passed June 15, 1881; and we therefore hereby state:—

1. The name of the said Corporation by which it shall be known in law shall be the "New York Pathological Society."

2. The particular business and objects of such society are the improvement of its members in Pathology and in Diagnosis and Treatment of Diseases as founded upon Pathology.

3. The number of Trustees, Directors, or Managers to manage

the same shall be six; and their names for the first year of its existence are:—

JOHN C. PETERS, M.D.,
T. MITCHELL PRUDDEN, M.D.,
WILLIAM P. NORTHRUP, M.D.,
LOUIS WALDSTEIN, M.D.,
L. EMMETT HOLT, M.D., and
JOHN H. HINTON, M.D.

4. The office and principal place of business of said Corporation shall be in the City, County, and State of New York.

Witness our hands and seals, this first day of April, one thousand eight hundred and eighty-six.

A. CLARK [L.S.]	L. WALDSTEIN [L.S.]
GUSTV. A. SABINE [L.S.]	LEWIS A. SAYRE [L.S.]
JOHN C. PETERS [L.S.]	WM. P. NORTHRUP [L.S.]
WILLARD PARKER [L.S.]	ALFRED L. LOOMIS [L.S.]
WESLEY M. CARPENTER [L.S.]	T. MITCHELL PRUDDEN [L.S.]
J. A. WYETH [L.S.]	GEORGE L. PEABODY [L.S.]
T. E. SATTERTHWAITE [L.S.]	A. JACOBI [L.S.]
J. C. DALTON [L.S.]	THOS. ADDIS EMMET [L.S.]
L. EMMETT HOLT [L.S.]	T. M. MARKOE [L.S.]
FRANCIS DELAFIELD [L.S.]	JOHN H. HINTON [L.S.]
GEORGE F. SHRADY [L.S.]	EDWARD G. JANEWAY [L.S.]

City and County of New York, ss.:

I hereby certify that, on the respective days hereinafter specified, before me personally came the following-named individuals, respectively; that is to say, on the first day of April, A.D. 1886:

ALONZO CLARK,	THOMAS M. MARKOE,
GUSTAVUS A. SABINE,	FRANCIS DELAFIELD,
JOHN C. PETERS,	GEORGE F. SHRADY,
WILLARD PARKER,	LOUIS WALDSTEIN,
WESLEY M. CARPENTER,	LEWIS A. SAYRE,
JOHN A. WYETH,	WILLIAM P. NORTHRUP,
THOS. E. SATTERTHWAITE,	ALFRED L. LOOMIS,
JOHN C. DALTON,	T. MITCHELL PRUDDEN,
L. EMMETT HOLT,	GEORGE L. PEABODY,
THOMAS ADDIS EMMET,	ABRAHAM JACOBI;

and on the second day of April, A.D. 1886:

JOHN H. HINTON and EDWARD G. JANEWAY.

who are severally personally known to me, and to me severally known to be the individuals described in and who executed the foregoing Certificate and they severally acknowledged to me that they executed the same for the purpose therein mentioned.

Witness my hand and seal, this second day of April, 1886.

S. B. GOODALE,

[L.S.] (99) *Notary Public,*
N. Y. County.

I approve of the within Certificate, and consent to the filing of the same.

New York, April 5th, 1886. C. DONOHUE,
Justice of the Supreme Court.

State of New York,
City and County of New York, } *ss.:*

I, JAMES A. FLACK, Clerk of the said City and County, and Clerk of the Supreme Court of said State for said County, do certify, that I have compared the preceding with the original Certificate of Incorporation of

The New York Pathological Society

on file and recorded in my office, and that the same is a correct transcript therefrom and of the whole of such original.

Indorsed, filed, and recorded April 5th, 1886.

In witness whereof I have hereunto subscribed my name and affixed my seal, this 5th day of April, 1886.

[L.S.] JAMES A. FLACK.

State of New York,
Office of the Secretary of State, } *ss.:*

I have compared the preceding with the original Certificate of Incorporation of the "New York Pathological Society," with acknowledgment thereunto annexed, filed, and recorded in this office on the sixth day of April, 1886, and do hereby certify the same to be a correct transcript therefrom and of the whole of the said original.

[L.S.] Witness my hand and the seal of the office of the Secretary of State, at the City of Albany, this sixth day of April, one thousand eight hundred and eighty-six.

FREDERICK COOK,
Secretary of State.

State of New York,
Office of Secretary of State, } *ss.:*

Filed and recorded April 6th, 1886.

DIEDRICH WILLERS,
Deputy Secretary of State.

CONSTITUTION.

ARTICLE I.

NAME, MEMBERS.

This Society, now duly incorporated under the laws of the State of New York, shall be known as the NEW YORK PATHOLOGICAL SOCIETY, and shall consist of active and honorary members.

ARTICLE II.

OBJECTS.

Its objects shall be the advancement of the knowledge of Pathological Anatomy, Histology, and General Pathology, and the improvement of its members in these departments, and in the diagnosis and treatment of disease as founded upon them.

ARTICLE III.

OFFICERS.

Its officers shall be a President, a Vice-President, a Secretary, a Treasurer, and an Editor of the Transactions, whose terms of office shall be one year; and six Trustees, two of whom shall be elected each year to serve for three years.

ARTICLE IV.

THE PRESIDENT.

The President, or, in his absence, the Vice-President, or, in his absence, a Chairman *pro tempore,* shall preside at all meetings of the Society, and shall have a casting vote. He shall preserve order, and shall decide all questions of order, subject to an appeal to

the Society. He shall also appoint all Committees authorized by the Society, unless otherwise specially ordered.

ARTICLE V.

THE SECRETARY.

The Secretary shall preserve minutes of the proceedings of the Society, and shall receive all histories, reports of Committees, and illustrations of specimens presented, and shall deliver the same into the hands of the Editor of the Transactions within six weeks after their approval. He shall issue notices of the meetings of the Society, and notify, in writing, members-elect of their election, and of the requirements of the By-Laws.

ARTICLE VI.

THE EDITOR.

The Editor of the Transactions shall collate from the material specified in the preceding Article such portions as may appear to the Committee on Publication of sufficient value to merit publication, and shall arrange them for the press, but the Society shall decide upon their publication after the Editor shall have submitted the estimated cost to the Trustees.

ARTICLE VII.

THE TRUSTEES.

The Trustees shall have the control and management of the financial affairs and funds of the Society, and no measure involving the expenditure of money, other than for the current expenses, shall be valid without the approval of the majority of the Board.

The Trustees shall render the Society, at the anniversary meeting in each year, a detailed report of their proceedings, and a particular statement of all moneys due, received, and paid out during the immediately preceding year, and of all outstanding trusts and obligations of the Society.

The Trustees, by a majority vote, shall fill any vacancy that may arise in their number, for the unexpired portion of the term of office.

ARTICLE VIII.

THE TREASURER.

The Treasurer shall take in charge all funds and trusts; shall collect all dues and obligations, and may employ an agent for that purpose at the expense of the Society; shall keep an account of all receipts and disbursements, and shall pay all just demands; but in the performance of these and all other duties of his office he shall be under the direction of the Trustees, and shall make no permanent investments without the approval of the majority of the Board.

He shall report to the Society at the anniversary meeting in January, and also to the Trustees whenever requested by them. He shall also report, at said meeting, the names of all members in arrears of dues, with the respective amount of their dues.

He shall be a Trustee and also a member of the Committee on Publication.

ARTICLE IX.

COMMITTEES.

1. *Committee on Admission and Ethics.*—The Society shall annually elect, by ballot, five of its members as a Committee on Admission and Ethics, to which all nominations for membership and questions relating to ethics shall be referred.

2. *Committee on Publication.*—This Committee shall consist of the Editor, the Treasurer, the Secretary, and two other members of the Society elected annually by ballot. The above Committees shall report to the Society annually at the anniversary meeting.

3. *Committee on Microscopy.*—The President shall annually appoint a Committee on Microscopy, which shall consist of three members of the Society.

This Committee shall have the care of the microscope, specimens, and instruments belonging to the Society, and shall examine all specimens referred to it, and report thereon in writing to the Society within one month.

ARTICLE X.

ANNUAL ASSESSMENT.

Any money that may be necessary to defray the current annual expenses of the Society shall be raised by a tax upon the members,

the amount upon each being recommended by the Treasurer and the Trustees, and sanctioned by a vote of the Society at the anniversary meeting in January.

ARTICLE XI.

AMENDMENTS.

This Constitution shall take effect immediately, and it shall not be altered except by a three-fourths vote of the active members present and voting at a stated meeting subsequent to one at which a proposition to that effect shall have been made in writing, and then only after the proposed alteration shall have been printed and sent to every active member of the Society.

BY-LAWS.

ARTICLE I.

MEETINGS.

The stated meetings of the Society shall be held at 8:30 o'clock on the evening of the second Wednesday of each month, except during the months of June, July, August, and September, when no meetings shall be held. Special meetings may be called by the Secretary, at the request of the President, or on a requisition signed by ten members.

ARTICLE II.

QUORUM.

Five members shall constitute a quorum for the ordinary business, and ten for the executive business of the Society.

ARTICLE III.

ORDER OF BUSINESS, STATED MEETING.

The order of business at the stated meetings shall be:—

1. Reading the minutes of the preceding meeting.
2. Report of the Committee on Microscopy.
3. Presentation of specimens with written or oral histories, with remarks thereon.

4. Executive Session at which shall be presented:
   a. The minutes of the last executive session.
   b. The Report of the Committee on Admission and Ethics.
   c. Any other executive business.
5. Adjournment.

ARTICLE IV.

ORDER OF BUSINESS, ANNIVERSARY MEETING.

The anniversary meeting shall be held on the second WEDNESDAY in January. The order of business at the executive session of this meeting shall be:—

1. Reading of the minutes of the last executive session.
2. Report of the Treasurer.
3. Report of the Editor and the Committee on Publication.
4. Report of the Committee on Admission and Ethics.
5. Election of the Officers, the Trustees, the Committee on Admission and Ethics, and the Committee on Publication.

ARTICLE V.

ELECTIONS.

1. All the Officers, the Trustees, the Committee on Admission and Ethics, and the Committee on Publication shall be elected by ballot and by a majority of the active members present and voting.

2. Two Trustees shall be elected annually for a period of three years at the anniversary meeting, according to the requirements of Article III of the Constitution, notice of which shall be given with the notice of the meeting.

ARTICLE VI.

REQUIREMENTS FOR ADMISSION.

The requirements for admission to membership in this Society shall be:—

1. That the applicant be a licensed physician in good standing or one who is engaged in fields of scientific work other than medicine, that is, those engaged in work in bacteriology, physiology, physiological chemistry, and other medical sciences.

2. That he present through a member, on printed forms prescribed by the Society, both an application for membership, and the

recommendation of three members of the Society, together with his diploma if he is not a member of either the Medical Society of the County of New York, or of the New York Academy of Medicine.

3. That he receive the assenting ballots of four-fifths of the members present.

ARTICLE VII.

MEMBERS ELECT.

A member elect shall not be entitled to the privileges of membership until he has paid the initiation fee; nor shall an election be valid longer than three months, unless these conditions are fulfilled. This shall not apply to honorary members.

ARTICLE VIII.

INITIATION FEE.

The initiation fee shall be five dollars. When a candidate shall be elected to membership of the Society at a meeting, within the calendar year, subsequent to the first meeting in October, the annual tax first required of such member shall be that of the year succeeding the year of such election.

ARTICLE IX.

RESIGNATIONS.

A resignation of membership shall not be accepted unless presented in writing, and after payment of all dues.

ARTICLE X.

REVISION OF CONTRIBUTIONS.

A member desiring to revise the history of his specimen, after it has been placed in the hands of the Editor, may receive it for that purpose, but must return the same to that officer within two weeks.

ARTICLE XI.

DUES.

The annual dues of active members shall be five dollars. The payment of one hundred dollars at one time shall exempt a member

from the payment of further dues. Those who have been members for twenty-five years or more are exempt from further payment, while retaining all the privileges of active members. Honorary members are not subject to dues.

ARTICLE XII.

UNPAID DUES.

All questions of indebtedness of members of the Society shall be referred to the Trustees, with power to act, or to report to the Society for its action. Any member failing to pay his dues after a period of one year and three months from the beginning of the fiscal year, without further notice, ceases to be a member of the Society; but upon payment of his indebtedness, he shall be reinstated without further formality.

ARTICLE XIII.

DISCIPLINE.

All questions of Ethics shall be adjudged in accordance with the Code of Ethics of the American Medical Association, and that of the Medical Society of the State of New York. There shall be three degrees of discipline, viz.; *Admonition, Suspension, and Expulsion.* A charge against a member for violating either of the aforesaid Codes of Ethics shall be made in writing, signed by the member making the charge, inclosed, sealed, and simply indorsed "Charge against a member," handed to the President, and by him submitted to the Committee on Admission and Ethics. The Committee shall furnish any member of the Society against whom a charge may have been preferred with a copy of the same, notifying said member and his accuser to appear before them, take testimony, and hear the defence.

Whenever the Committee on Admission and Ethics is prepared to report upon a charge against a member, the Secretary shall be required by them to notify the Society to that effect.

For *admonition,* a majority vote of the members present shall be sufficient; for *suspension,* a two-thirds vote of members present shall be necessary; for *expulsion,* a three-fourths vote of all members present shall be requisite.

ARTICLE XIV.

PRESENTATION OF SPECIMENS.

1. Members shall be called upon according to the order in which their names appear upon a register made on the evening of each meeting.

2. Members shall be allowed ten minutes for presentation of specimens, and this time shall not be extended, except by vote of the Society.

3. Every member shall be allowed five minutes for remarks on each specimen, and this time shall not be extended, except by a vote of the Society.

4. In discussions on specimens, members shall not be allowed to speak twice until all the members present have had an opportunity of taking part. A member shall not speak a third time, except by a special vote of the Society. This limitation shall not apply to mere questions and answers in the course of debate.

ARTICLE XV.

PRESENTATION BY CARD.

Specimens may be presented by card, and accompanied by a description. Their mode of presentation shall be left to the discretion of the President.

ARTICLE XVI.

ADJOURNMENT.

The Society shall adjourn at 10:30 P.M. There shall be no extension of the time, except by a special vote.

ARTICLE XVII.

AMENDMENTS.

These By-Laws shall take effect immediately. They may, by unanimous consent, be suspended at any meeting, but amendments shall be subject to the same requirements as those prescribed for amendments to the Constitution.

Proceedings

of the

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DR. HANS ZINSSER, *President*

THE HISTOPATHOLOGY OF CALCIFICATION OF THE SPINATUS TENDONS, AS ASSOCIATED WITH SUBACROMIAL BURSITIS

ELI MOSCHCOWITZ, M.D.

The lesion is a common one. It is a frequent cause of shoulder disability and, as such, it has long been and still often is mistaken for brachial neuritis, rheumatism, etc.

In this affection the shoulder is stiff and painful, the symptoms and the lesion itself developing soon, as a rule, after trauma. Neither the pain nor the stiffness is characteristic in extent or incidence. The pain may be continuous or intermittent, spontaneous or on motion referred to the shoulder itself, or, more often, to the outer or anterior aspect of the arm. It sometimes radiates

into the forearm or the neck. The stiffness may be manifested by awkwardness or by pain on motion. There is usually limitation of abduction, sometimes moderate, sometimes extreme. There is usually also limitation of rotation, internal, external or both. There is often tenderness in the upper deltoid region.

X-ray photographs of the cases studied showed well-defined areas of calcification within the spinatus tendons. These masses vary in size from a pea to a flattened nodule measuring 3–4 cm. in length. The masses may be single or multiple. The shadows are situated on the outer side of the tuberosity or head of the humerus, extending to beneath the acromion process.

PATHOLOGICAL EXAMINATION

The material studied consisted of tissue removed from three cases by Dr. Brickner.

CASE 1. A portion of the supraspinatus tendon removed sixteen days after injury. Section shows a crescentic mass of tissue. Covering the border is a fairly well organized granulation tissue. Within this zone and filling the entire cavity of the crescent is richly cellular early granulation tissue consisting of many round cells and plasma cells. There are a large number of newly formed cells and the remains of a recent hemorrhage. Filling the cavity, of which this section is an arc, is a mass of amorphous necrotic tissue in which are discrete deposits of lime.

Summary.—This section reveals substantially two stages of granulation tissue; an outer, the older, and an inner more recent variety. These inclose a necrotic focus which has partly undergone calcification.

CASE 2. Removed four months after injury. Due to imperfect orientation two separate masses are seen in the section. The first and larger consists of tendon fibers that have undergone hyaline degeneration in parts and in other parts calcification. From one aspect of the tendon there has sprung a large mass of granulation tissue, which is richly cellular, almost sarcomatous in appearance, consisting of large spindle shaped connective tissue cells with little fibrillar intercellular substance. In this tissue

there are numerous newly formed young blood vessels. There is abundant lime within this granulation tissue in the form of sharply circumscribed discrete masses; some of the masses are in immediate relation to giant cells.

The second and smaller mass consists of hyaline tendinous tissue which has undergone almost complete calcification.

Summary.—A tendon that has undergone extensive hyaline degeneration and calcification, with manifest necrosis and secondary calcification of the tendon. In addition there is recent granulation tissue, in which are imbedded numerous calcified granules.

CASE 3. Removed one and a half years after injury. The tendon shows essentially a mass of tendon tissue enclosing a cavity containing necrotic detritus. Between the tendon bundles there is abundant firmly organized granulation tissue. While many of the tendon bundles have undergone hyaline degeneration the necrotic tissue either is loosely within the cavity or is directly continuous with the surrounding tendinous area. No calcification is discoverable, although Dr. Brickner assured the writer that abundant gritty masses were found at the operation; the lime must have been shaken out of the specimen during transport.

Summary.—A tendon that has undergone partial hyaline degeneration and is infiltrated with abundant connective tissue. Necrosis of tendon.

DISCUSSION

These specimens exemplify three progressive stages of a lesion that may be termed a "tendinitis."

The first common factor is the formation of a new granulation that corresponds, according to morphological criteria, to the duration of the illness.

A second common factor is the presence of necrotic foci, which in two of our three cases were demonstrably calcified, and in the third probably so. The explanation of the necrosis is obvious. The blood supply of a tendon is notoriously meager so that only a slight tear or injury is necessary to completely cut off the blood supply.

The pathogenesis of calcification within tendons is governed

by the same conditions that apply to abnormal calcifications in other parts of the body. It has been definitely established that calcification occurs only in dead or inert tissues. It has thus a peculiar predilection for tissues that are necrosed or that have undergone hyaline degeneration.

The early calcification that has been noted in these cases (Dr. Brickner has seen cases in which X-ray shadows were demonstrable three days after injury) is remarkable, and can only be explained by the observation of certain experiments upon pathological calcification in other tissue of the body. For instance, Litten and Lick found lime in necrotic kidneys one day after ligation of the renal artery. Especially significant are the observations of Schujeninoff, who found calcification of muscle fibers 36 hours after suture of the divided muscle. Numerous experimental observations upon the healing and regeneration of tendons have been made, but these fail to throw any light upon the problem of calcification of tendons. This may be due to the fact that nearly all the observations were made upon the Tendo Achilles which may prove to be structurally different from the spinatus tendons. At all events, I am not aware of any disease of other tendons analogous clinically to the condition under discussion. In other words, the associated symptom-complex, namely, trauma, necrosis and early calcification of a tendon, attended by protracted disability, is apparently nowhere observed except in the spinatus tendons.

The only conditions to which this malady may be likened are the comparatively uncommon traumatic "ossifications" discoverable by X-ray in various tendons, especially around joints. To these may be added the "calcaneus sporn" arising from the posterior surface of the os calcis and extending into the Tendo Achilles; "Rider's bone" or "ossification" of the adductors of the thigh; and "Drill bone," or "ossification" at the insertion of the deltoid. Myositis ossificans is in all probability an allied condition. The possible objection that these shadows are bone and not lime does not entirely disqualify the parallelism. In the first place, pathological evidence that these shadows are bone and not lime is still

wanting. In the second place, it is now generally conceded that pathological ossification cannot occur without premilinary calcification, so that these shadows in their early stages must have represented deposits of lime. These lesions, however, cannot be compared either in the matter of frequency or in the early development of the lesion.

The lesion described in the spinatus tendons has, however, certain precise pathological analogies. We refer to the rare multiple nodes described in tendons by Krause and Trappe, Neuwirth and L'Hermitte, which are embolic in origin and are probably due to calcification of an infected focus.

The gouty deposits in tendons are also identical pathologically, the only difference being that instead of lime the deposit consists of urates.

Discussion:

DR. BRICKNER: Dr. Moschcowitz's presentation is especially interesting because it is the first systematic histologic study of calcareous deposits in the spinatus tendons and is based on the largest series of cases that have been studied surgically. I think we may say that we now have a clear notion of this variety of "shoulder disability" in its histologic and surgical aspects, but there remain many problems to be solved. Among these is the peculiar tendency of the supraspinatus, sometimes the infraspinatus tendon, to the early deposit, sometimes large and multiple deposits, of lime salts, after comparatively mild violence. I have seen twenty cases in the last couple of years.

I am not sure that Dr. Moschcowitz is justified in calling calcifying spinatus tendonitis the chief cause of shoulder disability, but I believe subacromial bursitis, which often has this tendon lesion associated with it, *is* the most common cause.

I use the term "shoulder disability" in preference to "stiff and painful shoulder" because either the pain or the stiffness may greatly preponderate or exist alone.

Codman first gave a very comprehensive description of subacromial bursitis, anatomically and clinically, and in two articles correctly located one of the varieties of deposit—the semi-fluid, extratendinous—as beneath the bursa, but he spoke of it as of a cyst, which is wrong, for there is no capsule or limiting membrane. Wrede, in the report of a single case, also located the deposit correctly, viz., in the supraspinatus tendon. Aside from these two, all writers on subacromial bursitis and tendon deposit have been in error. Indeed, the literature of this subject strikingly indicates the not uncommon tendency in medicine to jump at wrong conclusions, and the frequency with which fallacies are transmitted from one author to another.

Painter, who was the first to observe the calcareous deposit, reported that he evacuated it from within the bursa, although Codman, who was present at

the operation, observed that it came from beneath the bursa. In two other cases operated upon by Painter he found no deposit (because he did not look beneath the bursa), and he assumed that the X-ray shadow was produced by thickening of the bursal walls. Since then all surgeons and radiographists, excepting Codman and Wrede, have regarded these shadows as due to thickenings of, effusions in, or calcifications of the bursa. Holzknecht, for example, calls the calcareous mass a "bursalith." Cumston recorded one of these cases as a suppurative bursitis, although there was none of the familiar symptoms or signs of suppuration, and in spite of the fact that the "thick, yellowish pus" evacuated "from the bursa" was not examined. When, as is often the case, the bursal walls are adherent, an incision into the sac, unless made with this consideration in mind, is apt to go through the floor of the bursa, evacuating from beneath the often cheesy deposit, which thus appears to come from within the bursa. Baer, who also operated upon cases of subacromial bursitis not only repeats the error that "replacement of the bursa by scar tissue causes a shadow in the radiogram," but also assumed that "if the process is a tuberculous one the cavity may be filled with a dense, cheesy material." I have seen but a single, doubtful case of tuberculous subacromial bursitis. I have had one of these "cheesy" calcareous deposits studied bacteriologically; it was not only germ-free (smears and cultures), but also produced no reaction in guinea-pigs.

Another fallacy has been the assumption of bacterial or toxic irritation as an etiology of subacromial bursitis. Such an assumption has never been substantiated. If the condition were bacterial or toxic we ought to see it also in the olecranon, trochanteric and other bursæ. Excluding the rare tuberculous and the occasionally suppurative (septic) variety, subacromial bursitis (the bursitis of shoulder disability) is traumatic in origin, due, I believe, to bruising the bursa and the tendon between the head of the humerus and the acromion process. The trauma may be either an external or an internal violence. As instance of an external violence, a fall upon the outstretched arm, which jams the humerus against the acromion. A physician whom I operated upon this week, thrown by an automobile *upon* his shoulder (he says) seventeen days previously, had dense adhesions in the bursa and two discrete, large, dry, powdery calcareous deposits in his supraspinatus tendon. Very often there is no history of injury. In these cases the lesion results from mild internal violence, viz., a sudden or unduly vigorous abduction of the arm, as in the lurch of the body while hanging to a street-car strap, exercising on flying rings, leaning on the outstretched arm as in scrubbing the floor, etc. In all these forms of injury the bursa and tendon (supraspinatus, infraspinatus, or both) are compressed between the two bony surfaces. There results, as may be seen at operation, a hemorrhagic infiltration of these structures and, often, a small tear of the supraspinatus near its insertion, sometimes through its entire thickness. There is no doubt that a tear of this tendon can be produced by sudden abduction, in the adult. Codman reported three, and operated upon two, cases of complete rupture of this tendon. In one, a woman, it resulted from throwing a heavy blanket over a clothesline; in the other, a man, from tightening a saddle-girth. In both cases something was felt to snap, and the arm fell limp.

There are two forms of the calcareous deposit, in my experience,—one chiefly extratendinous, and associated with a tear in the tendon; the other, single or multiple, entirely within the tendon and with no surface indication of tendon injury. Either form, independent of the acuteness or chronicity of the case, may be semi-fluid or dry and gritty. While Dr. Moschcowitz is no doubt correct, as a pathologist, in calling this a "calcification of the tendon," surgically it is to be regarded only as a calcareous deposit. There is no extension, grossly, of the calcification beyond the torn fibers immediately surrounding the deposit.

We have both referred to the early appearance of the lime. I have operated upon cases sixteen and seventeen days after the injury, and I have seen the shadow of the deposit ten and five days and even, if the history was reliable, one day after injury.

The operative plan I follow consists in splitting the deltoid muscle, carefully incising the bursal roof, dividing all bursal adhesions, incising and dissecting up the floor of the bursa, removing the deposit from the surface or from within the tendon (usually the supraspinatus), trimming the edges of the tendon tear or incision, suturing the tendon, and then suturing, successively, the floor of the bursa, its roof, the muscle, and the skin, without drainage. I smear a very thin layer of vaseline in the bursa. The arm is abducted in plaster for about eight days.

GRAM-NEGATIVE MICROCOCCUS CAUSING FATAL ENDOCARDITIS

CALVIN B. COULTER, M.D.

(*Pathological Laboratory, Presbyterian Hospital*)

The presence in the blood stream of the gonococcus and meningococcus as a general bacteriæmia with septic manifestations has been observed repeatedly. In the case to be reported here, there was presented the familiar clinical picture of infective endocarditis with the recovery from the blood during life, and from the organs at autopsy, of a Gram-negative micrococcus which appears to be closely related to the gonococcus, but differs from it in important particulars, and represents probably a new species.

The patient, a Swiss cabinet-maker of 45 years, entered the Presbyterian Hospital November 6, 1914, suffering with dyspnœa and general weakness and repeated vomiting. The onset of symptoms had occurred three months previous with chill, fol-

lowed by progressive weakness and night sweats. The patient presented the signs of cardiac enlargement with a loud systolic murmur, and pulse of auricular fibrillation. The liver and spleen were enlarged. No petechiæ were found. Diagnosis of malignant endocarditis was made.

Blood Examination, Nov. 7.—Leucocytes, 8100. Polys., 69 per cent.; Monos., 28 per cent.; Eosin., 3 per cent. Blood culture, positive.

Disease ran an irregular febrile course, temperature reaching 103°–4°. There were recurrent attacks of tenderness over the spleen and associated with this on November 17 there was swelling and redness over the 5th left metatarso-tarsal articulation, and on December 2 swelling and redness appeared over right 1st metacarpo-carpal joint, with tenderness of pulp space of adjacent forefinger.

November 17.—Gonococcus complement fixation serum, anticomplementary.

November 27.—Leucocytes 12,200. Polys., 79 per cent.; Lymphos., 29 per cent.

December 7.—Leucocytes, 11,400. Polys., 81 per cent.; Lymphos., 18 per cent.; Eosino., 1 per cent.

Blood cultures were positive on November 7, November 11, November 13, November 27, November 30 and December 16. Last culture plates showed 6 colonies per c.c.

December 25.—The patient developed rather suddenly a left hemiplegia and died after about 36 hrs. with signs of cerebral hemorrhage.

At *autopsy,* 8 hrs. post mortem, was found an early bronchopneumonia of both lungs. The heart was large, weighing 520 grams, and showed hypertrophy and dilatation. The valves were normal, except for the mitral which showed on the margin of its posterior cusp a rounded and thickened tag of tissue, just large enough to contain a circular ulcer 6 mm. in diameter. This ulcer completely perforated the valve; its margins were firm and raised, its cavity filled with fibrin; in one spot it showed a minute vegetation. This small patch was the only evidence of vegetative endocarditis throughout the heart.

In the wall of the jejunum was found a small thrombotic nodule, 8 mm. in diameter. The liver and kidneys showed a state of chronic passive congestion. The pelvis of the right kidney contained pus. In several of the kidney glomeruli were seen in sections necrosis of a portion of a glomerular tuft, and later stages, with fibrosis and adhesions to the capsule, of the lesion considered characteristic of *Streptococcus viridans* endocarditis.

On a branch of the right middle cerebral artery was found an embolic aneurysm 7 mm. in diameter. Rupture of this had caused an extensive hemorrhage into the brain tissue, and had been the immediate cause of death.

Cultures at Autopsy.—Heart's blood: sterile. Kidney: sterile. Pyelitis: sterile. Lung: streptococcus and pneumococcus mucosus. Hemorrhage in brain: same organisms as found in lung. Spleen and the embolus in the jejunum: pure culture of Gram-negative micrococcus. Section through the ulcer on the mitral valve shows clumps of small cocci lying in the zone of fibrin just beyond the necrotic valve margin, and reaching the surface of the ulcerated area in one spot.

DESCRIPTION OF ORGANISM

The microorganism isolated appears as a very small coccus, in size equal to the smallest forms seen in the ordinary *Staphylococcus aureus*. There is hardly any visible variation in size between individuals in a given culture and in growths on the various media. Diplococcus forms are frequent and resemble in form the biscuit-shape of the gonococcus. Small clumps of three to eight are most numerous. Curious bacillary forms occur, the shorter of which can be resolved into a chain of four or five cocci, the larger appear homogeneous, and reach twice that length.

Stained by Gram's method with the meningococcus and hay bacillus on the same slide as controls, this coccus is invariably decolorized. Methylene blue and safranin alone stain it poorly. Fuchsin gives a more intense stain.

The first isolation from the blood was obtained on 1 per cent. dextrose-agar plates, poured at the bedside, but growth did not

occur in inoculations into dextrose-meat-infusion-bouillon. Attempts at isolation from the blood were made by other investigators, using media of the same formula, but were never successful. On blood plates the colonies appeared after 48 hours incubation at 37° C. Typical colonies were 0.5 mm. in diameter, dark green in color and surrounded by a diffuse zone of light olive green. On surface cultures the *characteristic delicate growth* is visible after 12–24 hours, and reaches its maximum at 48 hours. Colonies are always discrete, and macroscopically, are of two types: The smaller and more numerous are minute and almost invisible to the naked eye except when crowded together, where they give the appearance of a confluent growth. The larger colonies attain a diameter .25 mm., and appear as glistening transparent droplets. Microscopically, the colonies are alike, they are roughly spherical, dry, and appear made up of minute refractile granules. When a colony is touched with the needle it is easily dislodged, and moves about on the surface of the medium without breaking up.

Simple dextrose-agar was used successfully for the isolation from the intestinal embolus, and transplants in the second generation from the blood plates grew well in this medium. Growth did not occur at first on Loeffler's blood serum, but does so after artificial cultivation. Ascitic dextrose-agar is the most favorable medium, and after continued cultivation upon it the separate colonies are opaque, white, with wrinkled surface and outline, and tend to umbilication. They resemble minute bread crumbs. Under cultivation there is no increase in size of colonies. On the simple solid media no change has occurred, and growth appears as on first isolation.

In fluid media and in the water of condensation of solid media, growth is peculiar. After 8–12 hours discrete granular masses up to 0.5 mm. in diameter are noticed in the bottom of the flask, clinging to the sides of the glass. The supernatant fluid is perfectly clear. After 36 hours a general cloudiness begins and increases for 2–3 days. Old broth cultures show a delicate milk-white veil adhering tenaciously to the bottom and sides of the glass and a few delicate filaments springing from the veil float in the fluid.

Growth is as vigorous anaerobically as aerobically, and neither macroscopically nor microscopically do the two cultures differ.

Microscopically this organism appears like a minute gonococcus or meningococcus, but large involuted forms, metachromatic staining, and rapid autolysis, do not occur. The isolation upon serum-free media, and the vigorous growth throughout bouillon tubes, are important points of differentiation from the gonococcus. The firm dry colonies and spontaneous sedimentation in broth cultures make the organism resemble the *Micrococcus pharyngis siccus,* but the extreme delicacy of growth of this unclassified coccus is unlike that of any of the Gram-negative micrococci with which I am familiar.

Dextrose is the only sugar fermented. In litmus milk there is a slight change in color, but levulose and galactose used alone are not acidified. Thus the fermentation reactions suggest the gonococcus.

An immune serum was produced by intravenous injections of killed cocci into rabbits. This agglutinated the coccus in a dilution of 1:32 and very slightly in 1:64. This serum was tested against a strain of meningococcus with entirely negative results. A strain of gonococcus was agglutinated in 1:32 dilution. Portions of serum were then absorbed with the homologous coccus and the gonococcus. Serum absorbed with its specific coccus no longer agglutinated the gonococcus while after absorption with the gonococcus, it still agglutinated the specific coccus in dilution of 1:16.

The coccus was not agglutinated by the patient's serum, nor by a commercial antigonococcus serum, which however gave negative results with the gonococcus strain tested above, nor with a meningococcus immune serum.

This coccus is highly pathogenic for mice. One fifth of the 48-hr. growth on a blood agar slant killed a white mouse in 4 hours. The coccus was regularly recovered from the heart's blood of experimentally injected mice.

Guinea-pigs succumb in 12 hours to large doses intraperitoneally; chronic infections have not been set up, using smaller amounts of material for inoculation.

Similar results have been obtained with rabbits; small doses do not set up a chronic infection; large doses intravenously result in death in 60 to 72 hours. The organism has not been regained from the blood during life of experimental rabbits, nor from the heart's blood at autopsy, and it seems probable that death in guinea pigs and rabbits is due to the liberation of a toxin from the bodies of the cocci.

Attempts have been made to obtain a soluble toxin, by passing bouillon cultures, grown from periods varying from 48 hours to 10 days, through a Berkefeld filter. The filtrates have been uniformly non-toxic for white mice and guinea-pigs.

CONCLUSIONS

Morphologically, this organism seems related to the Gonococcus-Meningococcus group. Culturally, it does not conform with any organism with which we are familiar, although here too there are suggestive points of resemblance to the well-known Gram-negative diplococci. Accurate differentiation on the basis of serum reactions can not be made until an immune serum has been developed with an agglutination titer higher than 1 : 64, the maximum so far obtained. Preparation of such a serum has been rendered difficult by the toxicity of the coccus for rabbits.

CASE OF SUB-LEUKÆMIC LYMPHADENOSIS

MORTIMER WARREN, M.D.

(Pathological Laboratory, Roosevelt Hospital)

The title given to this case report is used more in a descriptive than in a diagnostic sense in an attempt to define the pathological conditions found.

In order to arrive at any kind of a diagnosis it is, of course, essential to know as much as possible of the clinical history and course of the patient, especially since the objective evidence is limited to the histological appearance of one lymph node and to

the blood findings. I therefore will give briefly the history and status of the patient.

Clinical History.—A white male of twenty-six years, born and brought up in the British West Indies,—a railroad clerk by trade,—entered The Roosevelt Hospital on June 5, 1914, service of Dr. Evan M. Evans, History No. D–6192. His chief complaint was weakness, gradually increasing for the past fifteen months; at times pallor and yellow color had been noted by his friends. For a week before admission he had some evening fever and slight sweats with chilly sensations. Past history is unimportant aside from that of malaria when in the British West Indies, with frequent dosage of quinine; he had, however, no chills.

Examination.—A young man of 116 pounds, with evident pallor and slight icterus. Moderate enlargement of axillary, inguinal and epitrochlear lymph nodes. Spleen edge is palpable 2¾ inches below costal margin. Liver edge not felt. Heart and lungs negative. No sore throat. There was a petechial spot in the soft palate which subsequently disappeared.

During his stay in the hospital from June 5 to July 3, 1914, examinations of urine were negative, aside from the presence of bile in one instance, and of urobilin in another. The gastric contents showed lack of free hydrochloric acid and the presence of occult blood. Fæces were negative for ova and parasites. Temperature was irregular ranging from 99° to 102°, but towards the end of his stay lessened in height. A blood culture was negative. Wassermann was negative.

On June 10, 1914, a pectoral lymph node was excised, section of which (B–7028) I wish to show and present for your opinion and diagnosis.

The *blood findings* were interesting, and were, I believe, directly related to the changes in the lymphatic apparatus as witnessed by the histological structure of the excised lymph node. Hæmoglobin, 54; leucocytes, 18,000; erythrocytes, 4,400,000. Polynucleus, 42.6 per cent. Lymphocytes, 12 ordinary lymphocytes; 19 stimulation forms; 18.6 pale cells. Transitional, 1. Eosinophiles 5.3. Mast cell, 1.3.

DISCUSSION

The leucocyte count was sub-leukæmic, being 10,000 to 20,000, with some forty-odd per cent. of mononuclears belonging to the lymphocytic series, with a constant increased per cent. of eosinophiles.

Anæmia was present at all times, more marked in the individual red blood cells than in the total count: of chlorotic type, with considerable pallor and variation in size, shape and staining reaction of the cells. Occasional normoblasts were seen. Platelets in smears were evidently increased.

At first we tried to make the leucocyte formula fit into the myeloid series but the individual mononuclears, though deeply basic in staining reaction of the protoplasm, were scanty in nucleoli and were non-granular. They gave no oxydase reaction and the blood was practically free from myelocytes or any cells which could be considered transitional forms in the neutrophilic group, though transitionals of the usual variety were present in fair number. The lymphocytes could be divided into three groups: (1) The ordinary small cell with its little protoplasm. (2) Large pale cells with azure granules,—likewise normal. (3) Abnormal deep, basic cells of the type of "stimulation" forms. Smears of the gland showed all the types of cells seen in the blood beside larger endothelioid cells.

Examination of sections led to a variety of diagnoses. I was inclined to some form of metaplasia at first,—later to the diagnosis of "Hodgkin's," a provisional diagnosis of which Dr. Mann had already made. This diagnosis was strengthened by the result of a growth from a portion of the node on egg media, which proved to be *Bacillus Hodgkinii*. Further study has, however, convinced both Dr. Mann and myself, as well as Dr. Cunningham, who has recently reviewed all our cases of Hodgkin's disease—some twenty in number—that this is not a proper diagnosis. Here I might say that Dr. Butterfield examined the smears of blood and sections of the gland and did not consider that it conformed to Dorothy Reed's description of Hodgkin's disease, but was unwilling to completely correlate the blood and tissue findings. A section of the

gland, a smear of the blood and a plant of the culture were sent to Dr. Bunting in Wisconsin, who reported both the gland and organism typical of Hodgkin's disease. He regarded the blood differential as rather higher in lymphocytes than usual, except in early cases of the disease.

The gland itself shows a varying fibrosis which is marked only in portions and is somewhat whirling in character. The follicles as such are not evident; there are, however, focal collections of large mononuclears showing active mitotic division,—areas which may represent the germinal centers and the cells of which may be germinal center cells. Similar cells are also scattered throughout the gland in the interstitial tissue, and are likewise seen in the capillaries and in the lymph spaces. These cells appear to me to be the source of the abnormal cells, the lymphocytic stimulation cells of the blood. There are larger cells with well marked nucleoli occurring singly in the interstitial tissue, and in areas there are pale staining, endothelioid phagocytic cells, but there are no multinucleated giant cells, or giant cells with lobed nuclei. The preponderating cell is a lymphocyte of the small type. Occasional mast cells and scattered eosinophiles are present. I think I can see all sorts of transition stages between the large, actively dividing cell and the small lymphocyte, in certain examples forming a characteristic plasma cell.

I believe this is a case of leukæmia of atypical form: It is evidently not acute—patient was heard from about two months ago and was then in fair condition—and it is not of the chronic type, unless in an early stage. A count made one week after leaving the hospital showed 55,000 leucocytes.

One can readily believe the anæmia to be secondary, possibly in part hæmolytic in character, thus accounting for the icterus and the urobilinuria, though there were no definite signs of active regeneration. It is, of course, impossible to draw any conclusions as to the state of the bone marrow.

Discussion:

DR. ZINSSER: I would like to ask Dr. Warren's views on the possible relation of this case to cases in which *B. Hodgkinii* is found.

DR. WARREN: We found this organism in a mediastinal sarcoma and in two or three tubercular lymph nodes. This one grew in pure culture in egg media.

DR. COULTER: I have cultivated a similar organism in Hodgkin's disease from the cervical lymph nodes, and in another case similar to this one of Dr. Warren's, from excised lymph nodes.

DR. TAYLOR: Doctor Pease has been making cultures at our hospital from various cases of glandular enlargement and has isolated by means of shake-cultures of glucose-ascitic-agar diphtheroid bacilli. These have been found in a number of cases of typical Hodgkin's and also in what was histologically lympho-sarcoma and a case which at autopsy was apparently tuberculosis. The possibility of a combination with Hodgkin's disease in this case could scarcely be eliminated, but it seemed to us that the whole process might be explained on a tubercular basis.

DR. WARREN: We have had frequent contaminations of blood cultures of a diphtheroid organism. Whether it is related to *B. Hodgkinii* I don't know.

DR. GARSIDE: In erysipelas I have taken the skin and rubbed it on the plate and got a pure culture of streptococcus. Dr. Bunting attempted to reproduce the disease, did he succeed?

DR. WARREN: He produced lymphatic enlargement and necrosis, but I don't think it is the same as in human beings.

DR. COULTER: Did the case run a febrile course?

DR. WARREN: 99 to 102.

ADENO-CARCINOMA OF UTERUS WITH METASTASES IN BOTH TUBES

L. W. STRONG

(*Woman's Hospital*)

I have an interesting case of adeno-carcinoma of the body of the uterus with metastases in both tubes. So far as I am aware there is no case in the literature of a double metastasis in the tubes. There are, of course, cases of cervical carcinoma with general metastasis, and there are cases of carcinoma spreading to the tubes by direct extension, but this case shows no connection between the original tumor and the metastases.

The point of greatest interest in the case is the method of occurrence of the metastases, whether by the blood or lymph stream or by creeping up of the cells from below, or possibly by a mul-

ticentric origin of the tumor. There is no evidence of extension by the lymph or blood stream in this case, nor is it easy to imagine that if that were the method of origin, the metastases should occur in the epithelium of the tubal mucosa without previous involvement of some lymphatic structure.

The slides bring out two points bearing on this question. The first is that there is a general inflammatory reaction in the entire genital mucosa which suggests the possibility that a chemical or other irritant may have caused a multicentric development. The second point is that the lumina of the fundal glands and tubal mucosa show groups of very large desquamated cells which look like carcinoma cells, and it is possible that these represent wandering cells which have embedded themselves higher up in the tubal mucosa. The cervical glands of this case show a picture which might well represent appositional growth, since there are glands one half of which present perfectly regular epithelium, while on the other side of the lumen the cells have every appearance of the carcinoma which is directly adjacent to them. This idea of appositional transformation has been generally discarded for the unicentric idea of carcinomatous growth. Schöttlander still holds to the appositional transformation. Ribbert, Borst and others hold to the unicentric origin, while v. Hansemann and Lubarsch think that both methods of origin are possible.

If carcinoma is always a definite entity there can be no such thing as appositional growth, that is, a transformation of cells at the border into carcinoma cells; but, the general belief is that carcinoma is not such a fixed entity, as indicated by the transitions between carcinoma and benign growths, as adenoma, and also by the transitions between carcinoma and the so-called precancerous changes, so often seen in the breast. It is these unexplained appearances which are the support of the appositional transformation idea.

AN INTRACUTANEOUS METHOD FOR TESTING THE VIRULENCE OF DIPHTHERIA BACILLI

ABRAHAM ZINGHER, M.D., AND DAVID SOLETSKY, B.S.

(From the Research Laboratory, Department of Health, New York City)

The testing of the virulence of isolated strains of diphtheria and diphtheria-like bacilli is important for a number of reasons, the following being probably the most important:

1. It has been found that 4–8 per cent. of individuals in localities where diphtheria is endemic are carriers of bacilli morphologically and culturally like the diphtheria bacillus, but non-virulent in 30–50 per cent. of the cases. At the Willard Parker Hospital, Wilcox and Taylor found that 4.5 per cent. of the cases admitted to the scarlet fever wards were bacillus carriers, and of the isolated organisms only one half were virulent.

2. According to Neisser individuals who become persistent carriers after an attack of diphtheria show only non-virulent forms in fully 20 per cent. of cases. Such individuals could be discharged from quarantine if this fact were established.

Morphologically, the non-virulent strains cannot be separated from the virulent, while in their sugar fermentation reactions the two types are in a majority of instances similar. Hence, the animal test must be employed for final diagnosis in doubtful cases. The method so far in vogue for testing the virulence of diphtheria bacilli has been to isolate the strain, grow it for 48 hours in ascitic broth (1 part ascitic fluid + 2 parts veal broth), and inject 1 c.c. of the broth culture subcutaneously into a guinea-pig. A control pig is injected with the same amount of the broth culture, and also a small quantity of antitoxin (0.5 c.c. of a 100 or 200-unit antitoxin, which cannot be used for other purposes). If the strain is a true diphtheria organism, the control pig will live, while the test pig will die in 2–3 days, and the autopsy will show the typical lesions of death from the effects of diphtheria toxin; that is, subcutaneous œdema at the site of injection, often extensive, congested and hemorrhagic adrenals, fluid in the pleural

cavities, congestion of the lungs with areas of partial consolidation.

This method is reliable, but an autopsy should be performed in all cases, in order to exclude death from other causes.

Recently M. Neisser has suggested that the virulence of cultures be tested in the following way: One loopful of a 24-hour Loeffler slant of the organism is suspended in 1 cc., 10 c.c., and 100 c.c. of physiological salt solution, and 0.1 c.c. of each suspension is injected intracutaneously on the abdominal surface of a guinea-pig. As a control some antitoxin containing 8 units per c.c. is added to an equal volume of the heaviest suspension, and 0.1 c.c. of the mixture is injected intracutaneously in the same guinea-pig. True virulent diphtheria bacilli will cause a local inflammatory lesion, with superficial necrosis, in 48–72 hours, the intensity of the reaction depending upon the number of injected organisms and their virulence. The skin at the site of the control injection should remain normal in appearance.

This method is analogous to that of Römer for the determination of small amounts of diphtheria antitoxin in sera. This consists of the intracutaneous injection of varying mixtures of the unknown antitoxic serum and a standard toxin; a slight excess of toxin produces a local necrosing lesion, while a neutral or over-neutralized mixture shows no effect on the tissues at the site of injection.

The method recommended by Neisser is fairly satisfactory, but, following his directions, we have occasionally noted that the direct addition of antitoxin to the bacteria in the control injection immunized the animals sufficiently to affect the test lesions to a considerable degree. If the amount of antitoxin added is diminished to avoid this general immunization, the local action of the bacteria is not completely inhibited, and lesions are found in both test and control areas.

For this reason the following modification of Neisser's method which has been found to be both reliable and economical is suggested.

Method.—Two guinea-pigs are used for the testing of from

4 to 6 different strains. One pig serves as a control and receives 0.5 c.c. of antitoxin (about 200 units per c.c.) intracardially at the time of making the tests, or intraperitoneally 24 hours before. The intracardial injection is the better, as it produces a complete inhibition of the local action of virulent bacteria in the control injections. The hair on the abdominal surface of each pig is removed, either by the application of a paste made of barium hydrosulphide, or preferably by simply pulling the hair out. This can be easily done, with less pain probably than is associated with the prolonged irritation following at times the application of the depilatory.

For the bacterial emulsion, a fresh 24 hour growth from an ordinary Loeffler slant is suspended in 25 to 30 c.c. of normal saline. It is important that the growth be not more than 24 hours old, since many of the bacteria die if the culture is kept for 48 hours or longer in the thermostat. Ice-box preservation of grown cultures also kills many of the organisms. Loeffler slants are used similar to those furnished by the New York City Department of Health for the purpose of diphtheria diagnosis. They should have a fairly uniform surface size and be sealed with paraffin to prevent drying of the medium. It is also important that the medium be not too acid, since excess of acid is apt to inhibit growth to a considerable degree.

Suspensions of the cultures to be tested are prepared in the above way, and 0.1 c.c. of each is injected intracutaneously into both pigs. For the purposes of injection the abdominal surface is divided into 4 to 6 areas, depending upon the size of the guinea-pig, and the injections are made as far apart as possible in order to avoid a fusion of the lesions. Four strains can be tested out on a medium-sized guinea-pig, and six on a larger one, without the danger of overlapping. A .5 c.c. or 1 c.c. Record syringe with a very fine steel (Burroughs Wellcome & Co. No. 3) or platinum iridium needle (Burroughs Wellcome Co. No. 22) is suitable for the injection. If the injections have been made properly a circumscribed elevation appears, which persists for 1 to 2 minutes.

The results of the tests are noted in 24 to 48 hours. Virulent strains produce a definite local inflammatory lesion, which shows a superficial necrosis in 48–72 hours. In the control pig the skin remains normal, when the injections are accurately carried out, With non-virulent strains, no lesion will be found in either control or test animal.

In this way, four cultures can be tested on two animals, as compared with eight animals necessary in the older way. By the use of large pigs, on whom six tests can be made, 10 out of 12 pigs can be saved, an advantage which is considerable when a large number of strains are to be tested.

We have tested by this method 20 non-virulent and 40 virulent strains of diphtheria bacilli, and the results obtained corresponded exactly with those obtained with the subcutaneous test for virulence.

A little practise is required for the proper performance of the injection; but with good technique, fresh Loeffler slants, and a proper 24-hour surface growth, the results will be found to correspond exactly with those obtained in the usual and less economical way for determining the virulence of diphtheria and diphtheria-like organisms.

We wish to thank Dr. Wm. H. Park, Director of the Research Laboratory, for many helpful suggestions in carrying on the work.

Discussion:

DR. HOPKINS: I would like to ask if necrosis could be produced by any other organism of this group, and were tests made to determine the specific action of the organism by using antitoxin as control.

DR. ZINGHER: The local action of the diphtheria bacillus and of its toxin is very characteristic, and no lesions were produced when the *Bac. Xerosis* or *Hoffmanni* and about twenty non-virulent strains of diphtheria-like bacilli were tested by the intracutaneous test on the pig. The action of antitoxin injected intracardially into the control animal was found absolutely specific in counteracting the action of the virulent diphtheria bacilli.

DR. LAMBERT: When the animals die, are the lesions in the adrenals absolutely characteristic; can they be mistaken for anything else?

DR. ZINGHER: The congested and hemorrhagic adrenals in the presence of the other typical lesions are considered characteristic of the action of the soluble toxin of the diphtheria bacillus.

DR. WARREN: What do you do with the guinea-pigs afterwards?

DR. ZINGHER: We keep them for one or two months and then use them for complement.

DR. JOHNSON: Was there any fluid around the pericardium?

DR. ZINGHER: In the test animals, the total amount of bacteria injected represents as a rule, a sublethal dose. We have found occasionally in the regular test of virulence a small amount of fluid in the pericardium.

DR. JOHNSON: Did you test the blood and pleural fluid to find the organism?

DR. ZINGHER: We have found bacilli once or twice in several examinations of the heart's blood post-mortem. According to Wright 5 per cent. of the animals show the presence of bacilli in the heart's blood. The pleural fluid was not tested.

DR. ZINSSER: I am surprised at the large number of non-virulent strains. I ran through eighty and found only a few non-virulent. They all fermented like true diphtheria. Is the absence of virulence in carriers only temporary, has this been tested, and can these strains be brought to virulence?

DR. ZINGHER: Among scarlet fever patients admitted during the past year to the Willard Parker Hospital, Wilcox and Taylor found that about one half of carriers showed non-virulent organisms. In those who became carriers in the wards after admission fully 95 per cent. of the strains were found virulent. The absence of virulence in the organisms in the carriers harboring non-virulent bacilli is probably permanent. Roux and Yersin are of the opinion that both types are present in cases of diphtheria, the preponderance of each strain, however, varying with the severity of the disease; but that during convalescence all virulent strains undergo a definite diminution in virulence. Graham-Smith, Loeffler, and Park and Williams believe that the individual virulence or non-virulence is permanent with the strain. Dr. Williams following the methods advocated by several who claim they made this transformation failed to obtain the change. We are attempting at present to change a non-virulent into a virulent strain, according to the method suggested by Thiele and Embleton for the *Bac. Hoffmani.* They claim to have changed such a strain to a virulent diphtheria bacillus.

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DR. HANS ZINSSER, *President*

AGGLUTINATION OF TREPONEMA PALLIDUM

HANS ZINSSER, M.D., AND J. G. HOPKINS, M.D.

We wish to report some recent experiments which demonstrate definitely the presence of immune bodies in animals immunized with cultures of treponema pallidum. The earliest attempts to demonstrate antibodies in syphilis were in general unsuccessful, Failure to obtain immune reactions was due doubtless in a large part to the fact that the earlier workers did not have cultures of the organisms to work with and that the suspensions of organisms obtained from syphilitic lesions were too poor in treponemata to make success possible.

Noguchi in 1912 obtained positive complement fixation reactions in the sera of patients with advanced syphilis but not in those of inoculated rabbits, when he used as antigen aqueous extracts of syphilis cultures or extracts obtained from rabbit lesions. Kol-

mer, Williams, and Laughbaugh soon afterward reported similar results, using extracts of concentrated cultures. Positive results were given by a considerable number of sera from cases of human syphilis, but much stronger reactions with the sera of rabbits treated with treponema cultures.

In the course of our work with the treponema we have immunized a number of rabbits with suspensions of the organism obtained by centrifuging fluid cultures, and in this way have obtained suspensions containing enormous numbers of treponemata. The suspensions before injection were killed by heating one half hour at 56° C. In testing the sera of these immunized animals against similar unheated treponema suspensions we have observed powerful agglutination, which was observable both macroscopically and under the dark field, one of our rabbits giving very marked agglutination in a dilution of 1:2000. We have observed the agglutination, both when using a suspension of our own Strain "A" against which the animals were immunized, and also with a suspension of N-1, a strain isolated by Dr. Noguchi. The sera of some normal rabbits also showed power to agglutinate the treponema pallidum, but we have not so far obtained this reaction in a dilution greater than 1:20.

EXPERIMENT I. (MACROSCOPIC)

Suspension Strain "A."

Serum Rabbit "609" (intravenously treated with five injections of "A" suspension ranging from 1 c.c. to 5 c.c.).

Each tube contained 0.5 c.c. of serum dilution and 0.25 c.c. of suspension.

	Serum 609. First Bleeding		Serum 609. Second Bleeding		Normal Rabbit Serum	
	2 hrs.	15 hrs.	2 hrs.	15 hrs.	2 hrs.	15 hrs.
Conc.	+++	+++	+++	+++	+++	+++
1:2	+++	+++	+++	+++	+++	+++
1:5	+++	+++	+++	+++	+++	+++
1:10	+++	+++	+++	+++	+++	+++
1:20	+++	+++	+++	+++	±	±
1:50	+++	+++	+++	+++	0	0
1:100	+++	+++	+++	+++	0	0
1:200	+++	+++	+++	+++	0	0
1:500	++	+++	+++	+++	0	0
1:1,000	±	0	Not		0	0
1:2,000	0	0	Set		0	0
1:4,000	0	0	Up		0	0
Salt Sol.	0	0	0	0		

We have not yet proceeded far enough with our experiments to determine whether these reactions can be obtained with the sera of syphilitic patients or with those of rabbits showing syphilitic lesions.

We submit the preceding protocol as an example of the macroscopic tests made with the sera of immunized and of normal animals.

A CASE OF MULTIPLE MYELOMA

W. G. MACCALLUM, M.D.

Clinical History.—B. C., a woman aged 53, was admitted to the Presbyterian Hospital December 5, 1915, complaining of stiffness of neck and shoulders. This appeared gradually during the past three months but was not associated with any pain. On admission neck was held very stiffly, apparently entirely on account of spinal rigidity, as the muscles were not tense. There was a deep groove in the ribs running parallel with the sternum just outside the costo-sternal junction. The ribs were easily moved or bent and on very slight pressure gave the impression of being crushed. Thoracic and abdominal organs showed nothing abnormal. The spine was held rigid throughout. Both femora and tibiæ showed outward and forward bowing. No tenderness anywhere.

Blood count, examination.—

Leucocytes	9,000
Polymorphonuclears	54 per cent.
Lymphocytes	41 per cent.
Hæmoglobin	80 per cent.

On December 18 she developed signs of pneumonia and died five days later. The urine showed a moderate amount of albumen with hyaline casts but no Bence Jones protein.

X-ray photographs showed atrophy of the cervical vertebræ with destruction and collapse of the third, fourth and fifth. Areas of rarefication were thus demonstrated in many of the other bones including especially the ribs and long bones.

At the *autopsy* there was found a widespread confluent lobular pneumonia. The alterations of especial interest concerned the bones.

The ribs were rarefied and softened to such a degree that in

most places they could be crushed easily between the fingers. They were especially thinned and greatly depressed on each side of the sternum and in these broad grooves nearly every one showed several fractures, often marked out by the growths of callus tissue.

The eleventh dorsal vertebra had collapsed to a certain degree, so that there was a slight angular deformity at that point. Three of the cervical vertebral centra had collapsed in the same way, bending the neck forward into a position in which it had become somewhat rigid.

One humerus was cut open and its cortex proved to be not more than 1 mm. in thickness, while the large narrow cavity was devoid of any cancellous lamellæ and filled with a mottled grayish red opaque marrow.

If we may judge from the X-ray photographs the same rarefication had occurred in the other humerus and in the bones of both forearms, as well as the femora tibiæ and fibulæ. No fractures had occurred in those bones and there was no sign of a tumor growth at any place. Many diagnoses were ventured to explain the rarefication of the bones and the many fractures but even at the autopsy the mere cellular character of the marrow exposed in the humerus did not suggest a tumor formation. The cut surfaces of the vertebræ were perfectly homogeneous and except for a slight opacity, not different from normal bones.

MICROSCOPIC FINDINGS

Smears from the marrow stained by Giemsa and Hastings' methods showed a remarkable uniformity of cells. Nearly all were rounded or oval cells of moderate size with rather deeply stained nucleus and practically no granules in the blue stained cytoplasms. There was found a pale halo around the nucleus. Occasional suggestions of basophilic granulations in small numbers were found.

Sections reveal a marrow composed in places of the normal cells in their usual arrangement, but nearly everywhere there were found compact masses of cells of one type pushing aside the normal marrow and extending everywhere into contact with the

bone. Many fragments of cancellous lamellæ were found isolated in such masses. This tissue which was composed of cells corresponding with those found to be predominant in smears did not as a rule inpinge directly upon the bone but seemed always separated from it by a thin line of cells flattened almost like endothelial cells, which may have been osteoblasts. Nevertheless the effect in causing the destruction and wasting of the bone was extraordinary.

The cells which make up this tumor tissue were not like the myeloblasts described as forming the tissue in a case with numerous myelomatous tumors published in the *Journal of Experimental Medicine* some years ago (Vol. 6) but resembled more closely plasma cells. Whether they correspond exactly with plasma cells it is difficult to say, but after observing recently two cases in the laboratories of Dr. Norris and Dr. Warren, in which the whole character of the growth was very similar to this except in that definite tumors were found, it seems that two distinct types of myeloma must be recognized. Of these one is composed of myeloblasts, the other of cells practically identical with plasma cells. The explanation of the absence of albumoses in the urine is not clear but there have been recorded several other cases in which the urine was free from these bodies.

AORTIC ANEURYSM PERFORATING SUPERIOR VENA CAVA

W. G. MACCALLUM, M.D.

Clinical History.—H. G., woman, age 33, was admitted to hospital fifteen times between January, 1913, and her last admission, in the summer of 1914.

She had led a dissipated life with much abuse of alcohol and tobacco and very possibly had had syphilis. She entered the hospital complaining of shortness of breath and swelling of heart, face and neck. Ten days before admission in January, 1913, patient felt that her face was swollen; the same night she woke up with a choking sensation accompanied by pain. The neck was much swollen and the face bloated.

The physical examination showed œdema of the upper part of the chest and great dilatation of the capillaries in that region. A tracheal tug was

felt. There were diastolic and systolic murmurs over the heart and a definite Corrigan pulse. The veins in the epigastric and hypochondriac regions were dilated and tortuous. Eye grounds normal.

During the next month the cyanosis and subcutaneous œdema in the upper part of the chest increased. There was a good deal of cough with rusty sputum.

In February of 1914 these conditions had become accentuated, marked dyspnœa and continuous murmur heard over the back as low as the fifth dorsal vertebra. There was a large accumulation of fluid in the right chest.

In May the superficial veins over the upper part of the chest were very prominent. Wassermann reaction positive.

June 16, 1914, admitted for the last time with still more exaggerated symptoms of the same character.

Death occurred on August 26.

At the *autopsy* the left lung was found to be a good deal compressed and to lie against the vertebral column. The heart was removed, together with the large vessels and the lungs and upon dissection it shows the following:

The heart itself is large, its walls somewhat thickened; the pulmonary artery is pushed forward by a saccular enlargement of the aorta beneath. This sac measures 5 to 6 cm. in diameter in each direction, so that the pulmonary artery is not really much compressed. The superior vena cava is delicate until it reaches the region of the auricle, where it becomes thickened and somewhat rigid and is adherent to the aortic dilatation. The thoracic portion of the aorta shows no dilatation or intimal change up to the end of the ascending arch. The large vessels of the arch pass off normally. They, like the aorta, are delicate and elastic.

On opening the heart and cutting through the aortic ring and the dilated aorta it is found that the left auricle is normal; the left ventricle dilated; mitral valves normal; its trabeculæ and papillary muscles flattened. Just beneath the aortic valves there are linear rough elevations which look like a beginning reaction to aortic insufficiency. The aortic valves themselves are fairly competent by the water test; their edges, however, are thickened and roll into a cord, so that insufficiency must have been possible, with dilatation, and probably existed all the time. Aortic orifice measures 7 cm. in circumference. The tricuspid and pulmonary valves are normal. Right ventricle is rather large; its walls

measure 7 mm. in thickness; left ventricular wall measures 19 mm. in thickness. Coronary orifices are normal. Just above the coronory orifice there is a sudden dilatation of the aorta which ends as suddenly with the precipitous edge at the upper end of the ascending part of the arch. It is nowhere roughened or covered by thrombi, but the inner surface is very irregular and there are numerous small sacculations as if new small aneurysms started out from the wall of the old one. One of these, about 12 mm. in diameter, arises from the lower posterior part of the main aneurysmal sac and extends over toward the superior vena cava and presses against it; indeed, it practically pierces a way through the middle of the vein and divides it into two channels, fusing with the further wall of the vein, so that it looks like a bridge across the cavity of the vena cava, when it is exposed by opening that vessel. The blood was forced to pass on each side of this bridge and the two channels must have been still further narrowed by the thickening of the vein wall at this level. They now measure about 10–15 mm. in diameter. Under such circumstances there was no connection between the aortic lumen and that of the vein, since the aneurysmal saccule merely pushes its way through the middle of the vein to the opposite side; nevertheless it undoubtedly caused a good deal of obstruction to the return of blood from the head.

But the aneurysmal sac is found to have burst laterally as it passed across the vein, and a probe from the main aneurysm into the saccule emerges into the vein through a hole which proves to be in the wall of the bridge turned uppermost. This aperture is surrounded by a thrombus on the venous side and it was obviously through this that the blood rushed.

One receives the impression that this actual perforation may have taken place rather recently but the symptoms which it could have produced, such as murmurs and cyanosis, were already present to such a degree on account of obstruction of the vein and the valvular murmurs that it is surprising that the diagnosis could have been reached so accurately as it was.

PROGNOSIS IN PELLAGRA

A Preliminary Note

J. F. SILER, M.D., P. E. GARRISON, M.D., AND W. J. MACNEAL, M.D.

(From the Robert M. Thompson Pellagra Commission of the New York Post-Graduate Medical School and Hospital)

This is a preliminary report based upon the records of 1,162 cases of pellagra, all the cases which have been ascertained to have existed in Spartanburg County, South Carolina, up to October 15, 1914. We shall consider the prognosis first in regard to death rate in first year of the disease, or the year of initial attack, second in respect to liability of the survivors to have a recurrent attack in subsequent years or to escape further attacks, and third, the death rate in recurrent attacks. In each instance we shall inquire into the influence of race, sex and age upon the prognosis.

The gross death rate in the year of initial attack is shown in Table I.

TABLE I

Death Rate in Initial Attack of Pellagra

Year	Recorded Initial Attacks	Recorded Deaths in Year of Initial Attack	Indicated Death Rate, Per Cent.
Before 1908	56	13	23.2
1908	20	2	10.0
1909	57	15	26.3
1910	141	29	20.6
1911	229	32	14.0
1912	208	27	13.0
1913	242	37	15.3
1914	209	30	14.4
Total.....	1,162	185	15.9

The indicated death rate for the last four years is undoubtedly more accurate than for the earlier years, and we may say that in Spartanburg County about 14 per cent. of pellagrins die in the year of the onset of the disease.

Of the total 1,162 patients, no less than 977, or about 84 per cent., survived the year of the initial attack of pellagra, so far as these records go. Of these there were 179 cases originating in 1914, for whom the record of the first year is incomplete, and

there were 101 patients who passed from observation. There remain, therefore, 697 pellagrins concerning whose subsequent histories we have some recorded data. In the aggregate, the records of these 697 patients show 1,037 instances of recurrence in subsequent years and 591 instances of freedom from recurrence, indicating roughly that those who survive one attack of pellagra have about one chance in three of escaping an attack of the disease in the following year. All cases are here considered together. Some have been followed for ten years, others for only one year; some have recurred every year, others have never shown any recurrence; others have passed one or two years in good health and have then suffered recurrent atacks, while others, again, have had one or more recurrences with subsequent freedom from the disease.

Recovery from pellagra is very difficult to recognize with certainty. Of the 711 recorded cases which originated previous to 1913, there are 91 instances of pellagra in the initial year with subsequent freedom from recognizable evidence of the disease for at least two years. These cases may, with some reservation, be designated as instances of recovery after the initial attack. The indicated rate for recovery after one attack is, therefore, 12.8 per cent. This indication must be taken with some reserve, however, because there were recorded 13 patients who again suffered an attack of pellagra after an interval of two years without recognizable evidence of the disease.

The gross death rate in the year of recurrent attack is shown in Table II.

TABLE II

Death Rate in Recurrent Attack of Pellagra

Year	Recorded Recurrent Attacks	Recorded Deaths in Year of Recurrence	Indicated Death Rate, Per Cent.
Before 1908	80	7	8.8
1908	22	2	9.1
1909	34	5	14.7
1910	58	7	12.1
1911	140	29	20.7
1912	226	32	14.2
1913	233	29	12.4
1914	244	19	7.8
Total.....	1,037	130	12.5

The death rate in recurrent attack is apparently somewhat less, but, on the whole, not significantly different from the death rate in the initial attack.

The correlation between race and prognosis in pellagra is indicated in Table III.

TABLE III

Relation of Race to Prognosis in Pellagra

	White Race	Negro Race
Recorded initial attacks	1,010	152
Recorded deaths in initial attack	121	64
Indicated death rate, per cent.	12.0	42.1
Recorded recurrent attacks	970	69
Recorded deaths in recurrent attack	107	23
Indicated death rate, per cent.	11.0	33.3
Recorded cases incident before 1913	630	81
Recoveries (after one attack)	84	7
Indicated recovery rate, per cent.	13.3	8.6
Recorded cases incident before 1912	450	53
Recurrence for three consecutive years	210	19
Frequency of chronic pellagra, per cent.	46.7	35.8

Those cases tabulated as recoveries were free from evidence of the disease for two years subsequent to the year of onset.

It would appear that the negro race in Spartanburg County has suffered much more severely from the acute type of pellagra, showing a much higher death rate, although as we have shown in previous papers, the negro race, as compared with the white race, is very much less frequently attacked by the disease in this county.

The correlation between sex and prognosis in pellagra is indicated in Table IV.

It would appear that the attack of pellagra is somewhat more decisive in males than in females, as the former show a higher death rate in both initial and recurrent attacks and also a higher recovery rate after the initial attack. Chronic recurrent pellagra, on the other hand, is relatively more common in females.

TABLE IV

Relation of Sex to Prognosis in Pellagra

	Females	Males
Recorded initial attacks[1]	816	345
Recorded deaths in initial attack	123	62
Indicated death rate, per cent.	15.1	18.0
Recorded recurrent attacks	757	282
Recorded deaths in recurrent attack	84	46
Indicated death rate, per cent.	11.1	16.3
Recorded cases incident before 1913	501	209
Recoveries after one attack	59	32
Indicated recovery rate, per cent.	11.8	15.3
Recorded cases incident before 1912	365	137
Recurrence for three consecutive years	175	54
Indicated frequency of chronic pellagra, per cent.	47.9	39.4

The correlation between age and prognosis in pellagra is indicated in Table V.

TABLE V

Relation of Age to Prognosis in Pellagra

Age	0–12	12–20	20–40	40–60	60 and Over
Recorded initial attacks[1]	207	86	533	250	67
Recorded deaths in initial attack	6	13	69	60	27
Indicated death rate, per cent.	2.9	15.1	12.9	24.0	40.3
Recorded recurrent attacks[2]	105	51	557	229	91
Recorded deaths in recurrent attack	4	6	60	43	15
Indicated death rate, per cent.	3.8	11.8	10.8	18.8	16.5
Recorded cases incident before 1913	97	61	327	171	42
Recoveries after one attack	31	12	34	13	0
Indicated recovery rate, per cent.	32.0	19.7	10.4	7.6	0.0
Recorded cases incident before 1912	49	44	239	130	31
Recurrence for 3 consecutive years	23	20	124	49	12
Relative frequency of chronic pellagra, per cent.	46.9	45.5	51.9	37.7	38.7

The comparatively good prognosis in children is clearly evident in the table.

[1] One child has been omitted here because sex was not recorded.

[1] Nineteen cases omitted because age was not recorded.

[2] Four instances of recurrences omitted because age was not recorded.

Perhaps a few words should be said about insanity in pellagra. This topic has recently been discussed by Singer,[1] working in collaboration with us. He found mental disturbance in about 40 per cent. of cases of pellagra, chiefly symptomatic depressions and delirious states due to the intoxication of the disease, most commonly observed in men aged 21 to 40 and women aged 41 to 60. Such mental disturbance indicates a severe attack of the disease, but it clears up completely if the patient survives. Pellagra is much more common in individuals of faulty nervous organization, but chronic insanity or chronic nervous disease, due strictly to the pellagrous intoxication, if it occurs at all, is very uncommon.

AMŒBAS IN THE MOUTHS OF SCHOOL CHILDREN

ANNA WESSELS WILLIAMS, ANNA I. VON SHOLLY, AND CAROLINE ROSENBERG

(*From the Bureau of Laboratories, New York City Health Department*)

Since the announcement last summer by Smith and Barrett that an amœba genus, called *Endamœba* first by Joseph Leidy in 1879, is probably the cause of pyorrhœa alveolaris, and that an amœbicide, emetin, will cure the disease, interest has been stirred anew in the etiology and treatment of septic mouth conditions.

Among others, the Bureau of Laboratories of the New York City Health Department has begun a study of focal mouth infections helped by the interest and financial aid of Dr. Merritt, and this short paper is a first report of one phase of our study.

Soon after our observations were begun, we found that all cases presented to us by the several dentists who are collaborating with us, already had pus pockets formed in the teeth alveoli—that is, they were well-established cases—and when we began to inquire for beginning cases, we learned that the diagnosis of pyorrhœa alveolaris is made by most dentists—as is the diagnosis "trachoma" by most ophthalmologists—after the disease has made decided progress, so we decided to hunt for beginnings in school children.

[1] Archives of Internal Medicine, 1915, XV, 121.

The school in which we had done most of our intensive trachoma work was chosen for starting our examinations. So far, about 475 children between the ages of 9 and 16 years have had a preliminary examination and, from 150 representative ones, stained smears have been made and examined for amœbas.

The 475 children have been divided roughly into those having healthy-looking gums and those having receding or spongy and bleeding gums. The healthy-looking gums were further divided into those with one or more decayed teeth, and those with apparently sound teeth. Needless to say, we found very few of the latter, that is, of those with apparently healthy gums and sound teeth—about 1 in 8. About one half showed unhealthy gums. The exact figures will be given later.

Results of Smear Examination of 150 Cases.—From most cases two smears were taken. The smears were made as follows: In the bad cases, the teeth and gums were cleaned with a cotton swab dipped in 50 per cent. alcohol; then with the flat end of a hardwood sterile toothpick, material was scraped from the margin of the gums and stroked lightly over a clean glass slide making 3 or 4 streaks. The slide was then fixed while still moist by dropping methyl alcohol on it, and it was ready to send to the laboratory. This was called the superficial smear. A second toothpick was used to get material from beneath the margin of the gums, from which another smear was made and fixed. This was called the deep smear. In the cases with clean teeth and tight healthy-looking gums, the first smear was made before cleaning with alcohol. All of these smears were stained with Giemsa's stain by A. G. Mann of our laboratory, and were examined by us for amœbas. In regard to the identification of amœbas by stained films, I would say that they are more certainly and easily identified by this method than by warm living preparations, though, of course, both methods should be used in studying all of the characteristics of these microorganisms.

Stained by Giemsa, the delicately but definitely reticulated cytoplasm of the amœba stains a clear blue, while the small nucleus shows rounded or irregular masses of red granules and threads, with often a central vacuole-like body. This nucleus without

doubt corresponds to that most frequently described for *Entomœba histolytica,* but since we know that amœbas are notoriously variable in their entire morphology, according to their stage of development and to the conditions of growth, no definite opinion should be expressed as to the species of the forms found in these mouths until much further study has been made. The amœbas usually contain masses of undigested materials. They seem to take up very readily leucocytes, red blood cells, and many kinds of bacteria. I have placed a smear under the microscope from one of these cases.

Number and Percentage of Amœbas Found in Each Group of Children

I.	Healthy gums	$\left\{\begin{matrix}+6\\-14\end{matrix}\right\}$	= 30 per cent. positive
II.	Healthy gums	$\left\{\begin{matrix}+11\\-11\end{matrix}\right\}$	= 50 per cent. positive
	Decayed teeth		
III.	Tartar and Receding gums	$\left\{\begin{matrix}+37\\-10\end{matrix}\right\}$	= 84 per cent. positive
IV.	Spongy and Bleeding gums	$\left\{\begin{matrix}+61\\-4\end{matrix}\right\}$	= 94 per cent. positive

+, positive; —, negative.

Of course, we can say nothing definite yet as to the significance of the amœbas in these mouths. Finding them so often in apparently healthy mouths and in such young children does not agree with the statements of Bass and Johns and of Barrett, that they are not found in healthy mouths. They base their statements on the fact that they were not able to demonstrate amœbas in healthy adult mouths. The demonstration by Le Wald before this society in 1907 of amœbas in the mouths of healthy individuals, cannot be discussed in this connection since the condition of the mouths and the ages of those examined were not stated.

Moreover, we have so far made only one examination. Further investigation may show a larger percentage of amœbas constantly in the healthy mouths and a smaller percentage constantly in the unhealthy ones.

But these results as they stand are very striking, especially when we must add that most of the cases of spongy and bleeding gums show more amœbas in the films than the other cases. If

we could only rule out other microorganisms the evidence for the pathogenic action of the amœbas would be strong.

We have, however, a marked opportunity to test the prophylactic effect of ipecac or its emetin alkaloid.

We propose to divide the cases showing amœbas into groups, one to be watched without treatment and others to be treated in different ways. We shall have a tooth wash made up containing a dilution of one of these drugs, and have the cleaning of the teeth done morning and afternoon in the school clinic under the supervision of the school nurse. We hope by combining these practical investigations with the laboratory studies that we may be able to help demonstrate the relationship of these amœbas to septic mouth infections.

Discussion:

DR. MERRITT: I had not the slightest idea of being asked to speak on this subject. I have for a long time been interested in the question of the etiology of pyorrhœa. We had very positive statements made in Philadelphia last July regarding the relation of amœbæ to the disease which has puzzled many practitioners. We thought we would get the research laboratory to find out how much truth there was in the matter. Bass and Johns have made such positive statements that it is important to know whether they are true or not. The indiscriminate use of emetin, too, ought to be checked.

I do not think that the etiology of pyorrhœa depends on endamœbæ. The numbers of amœbæ found, I do not think, bear any relation to the advance of pyorrhœa. The most advanced cases I have seen had the least and the most simple one, most. The more healthy mouths as a rule seem to have amœbæ. The fact that so many are found in the mouths of children is perhaps the best evidence that they have little to do with the etiology of pyorrhœa. Pyorrhœa is certainly not a children's disease. I have seen reports of cases in children, but personally have never seen the disease in a person under 18 years. Amœbæ are found not only in mouths not kept very clean, but also in mouths carefully kept.

DR. LE WALD: Some years ago I found amœbæ in the mouth of a dentist extremely careful of his teeth. This discovery was made in the examination of the mouths of a large number of cases in the Philippines. The natives showed amœbæ in 75 per cent.; Americans, 71 per cent. In negative cases a repeated examination often resulted in positive findings. Thus I concluded that amœbæ were present in all mouths. Some of these people had carious teeth but not all. I concluded that amœbæ were constant inhabitants of the mouth. I have seen no reason to change that opinion.

DR. ZINSSER: In examining pyorrhœa cases we have found a great many spirochætes where the pus was taken from the gums. I think that is because of the presence of necrotic tissue, as in Vincent's angina.

DR. WILLIAMS: I should like to emphasize the question of the beginnings of the disease. Dr. Merritt says the earliest case he knows was 18 years. These children were from 9 to 16 years. Sixty-five of them had spongy, bleeding gums, slightly receding, with a great accumulation of leucocytes. The question is, are some of these beginning cases of pyorrhœa alveolaris?

DR. MERRITT: While there is usually a mild gingivitis in pyorrhœa, the disease affects essentially the alveolar bone. I, therefore, do not regard Dr. Williams' cases as true pyorrhœa. I think with proper care of the teeth pyorrhœa would never develop. One may have considerable loss of bone from the abrasive action of the tooth brush with no disease, or pyorrhœa with considerable loss of bone in addition to the gingival condition which accompanies it.

DR. KRUMWIEDE: I believe Dr. Williams found in these children as well as in pyorrhœa cases in adults enormous numbers of spirochætes with the amœba.

DR. WILLIAMS: Yes, in practically all mouths of these children except the most clean there were large numbers of spirochætes as well as many other varieties of microörganisms.

A BRILLIANT GREEN AGAR FOR THE ISOLATION OF TYPHOID BACILLI FROM FÆCES

CHARLES KRUMWIEDE, JR., M.D.

(From the Division of Laboratories, Department of Health, New York, N. Y.)

During the last year we have accumulated a great deal of data concerning the action of brilliant green on the growth of members of the typhoid-paratyphoid-colon group, when the dye is used in fluid and solid media. We hope to report the data shortly. At this time, I shall only describe a new plating medium for the isolation of the typhoid bacillus from stools.

The basis for the medium is an agar consisting of water, 1,000 c.c., Liebig's extract of beef, 3 grams, peptone, 10 grams, salt, 5 grams, and agar 15 grams. As this agar is used also as the basis for Kendall's modification of the Endo medium, we have found it most convenient to have the reaction made slightly alkaline to litmus, and to keep the medium in bottles of 100 c.c. amounts. To 100 c.c. of the melted agar is added 1 c.c. of the Andrade indicator (consisting of 100 c.c. of a 0.5 per cent. watery solution of acid fuchsin decolorized by the addition of 16 c.c. of

normal soda solution). The indicator keeps well and is not affected by light. Normal acid is then added till the agar is distinctly red. The correct point is reached when the hot agar is red but the color disappears on cooling. Having determined the correct amount for one bottle, this is noted and a similar correction made for the bottles of this batch of agar as used. This method has the advantage over setting the reaction of the agar in bulk in that variations are possible, should they seem necessary.

One per cent. of lactose and 0.1 per cent. of glucose are then added, using sterile 25 per cent. solutions of the sugars. After mixing, the brilliant green is added. We are now using two concentrations of the dye. To one bottle is added 0.2 c.c. of a 0.1 per cent. solution, giving a final dilution of 1 : 500,000, and to another is added 0.3 c.c., giving a dilution of 1 : 330,000. Each bottle is sufficient for six plates, as the layer of agar must not be too thin. The plates are left uncovered until the agar is hard, and then covered with porous tops. The medium is inoculated by surface streaking.

On this medium, the typhoid colony is very characteristic. With the light passing obliquely through the plate, they have a peculiar snow-flake appearance. Using a hand-lens with artificial light, they have the texture of a coarse wool fabric.

The brilliant green inhibits the growth of many of the bacteria in the feces, and in this way gives a relative enrichment of the typhoid bacilli, if present. The degree of inhibition of the fecal types depends on the flora and varies widely.

Two dilutions of the dye are used to obtain the maximum inhibition of the fecal flora and still insure good growth of the typhoid bacilli, which vary somewhat in their reaction to the dye. Endo plates should be planted as well. Although we have never failed to isolate typhoid bacilli from the green dye agar when they were present on the Endo medium, a much greater experience is necessary before we can be sure that some strains of typhoid may not be exceptionally sensitive to the dye and therefore fail to grow. Any change in the constituents of the medium may upset the balance, and require a readjustment of the amount of necessary dye.

Testing the medium by adding traces of carrier stools to normal stools, we obtained the following results. Of 130 such mixtures, 71 gave negative results on Endo. Of these, 48, or 67 per cent., were positive on the green dye agar containing 1 : 500,000 of the dye. In another series of 28 stools, both strengths of dye were used. Of these stools, 18 were negative and 10 positive on Endo; 9 were negative and 19 positive on dye agar containing 0.2 c.c. and 3 were negative and 25 positive on dye agar containing 0.3 c.c. One gave negative results with dye agar containing 0.3 c.c. due to almost complete inhibition of growth, but was positive on dye agar containing 0.2 c.c. Nine stools obtained for diagnosis during a localized epidemic gave similar results. All were negative on Endo, 4 were positive on the dye agar containing 0.2 c.c. and 5 on the dye agar containing 0.3 c.c.

Discussion:

DR. ZINSSER: In the preparation of typhoid media one difficulty we have found is the uniformity of production of media. In the green media is there any difficulty in getting uniform preparations? Is the dye constant?

DR. KRUMWIEDE: We have used the preparation of one manufacturer. Brilliant green, extra crystals, No. 366, Bayer. It is more uniform than the malachite green.

DR. ZINSSER: How is the media titrated?

DR. KRUMWIEDE: We have made the medium alkaline to litmus. The Andrade indicator gives a red color in hot media and is colorless when cold, when the correct point is reached; as a rule, 5 normal Hel. is required to bring it to that point when originally alkaline to litmus.

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CONTENTS

DR. HANS ZINSSER, *President*

THE ETIOLOGY OF TYPHUS EXANTHEMATICUS[1]

I. BACTERIOLOGICAL STUDIES

HARRY PLOTZ, M.D.

Abstract[2]

In a preliminary communication published in the *Journal of the American Medical Association,* May 16, 1914, I described an organism which I considered to be the etiological agent in typhus exanthematicus. The organism, a bacillus, was recovered from the blood of five cases of European epidemic typhus fever and of six cases of the mild endemic form of the disease known in the

[1] From the Pathological Laboratory, Mount Sinai Hospital, New York. For the financial support of these investigations, we are indebted to two contributors who desire to remain anonymous.

[2] A complete report will be published shortly in *The Journal of Infectious Diseases.*

United States as Brill's disease.[3] Since that time I have had the opportunity of studying a much larger series of cases with the same cultural methods, and the results, together with the serological and experimental studies, have confirmed the opinion then expressed. At the present time, we shall give only those data which bear upon the question of etiology, leaving other phases of the work for future reports.

The findings of previous investigators will not be discussed because none corresponds to the organism which I have found.

The differentiation of the mild endemic form of typhus fever seen in New York from other fevers, especially short term typhoids, is due to the clinical insight of Dr. Nathan E. Brill. Its similarity to typhus fever was later noted by Louria and G. A. Friedman. Following this came the striking cross immunity experiments of Anderson and Goldberger, which demonstrated that the disease described by Brill was most likely a mild form of typhus fever.

My studies were begun with the endemic form of the disease, using the viewpoints that had been established regarding typhus fever.

It had been demonstrated by early experiments that the virus exists in the circulating blood during the febrile period of the disease. It was also evident from previous studies that the virus was not filterable. Ricketts and Wilder searched the blood microscopically and saw a bacillus which they described. There is no evidence that the bacillus seen by them is the same as that which forms the basis of this report. Fried and Sophian could find no organisms in smears of blood made from five cases of endemic typhus fever.

It was surmised that because typhus fever had been proved to be an insect-borne disease, a protozoan origin would needs be found, but Ricketts and Wilder, in refutation, pointed out that the organism could be bacterial.

[3] As these studies give the definite proof that the cases of European typhus fever and the cases of "Brill's disease" are due to the same organism, we shall designate the European cases, *epidemic* typhus fever, and the New York cases, *endemic* typhus fever.

Aerobic cultures of the blood had been made by a number of observers, but as these had all been negative, I decided to use anaerobic methods.

Up to the present time, eleven cases of European epidemic typhus fever and forty cases of the local endemic form of the disease have been studied. I am indebted to Dr. Joseph J. O'Connell, Health Officer of the port of New York, for the privilege of studying the epidemic typhus cases and to the attending physicians of Mount Sinai Hospital for studying thirty-six of the forty endemic cases.

This work, as well as the investigations which form the basis of the subsequent papers, was carried out under the direction and with the helpful assistance of Dr. E. Libman. It was the energy and stimulus which he supplied to the work which helped us to carry it to a successful conclusion.

We wish also to thank Dr. F. S. Mandlebaum, pathologist of the hospital, for many courtesies and for placing all the facilities of the laboratory at our disposal.

METHODS OF CULTURE

Aerobic Methods.—Fifteen cubic centimeters of blood are withdrawn and inoculated into flasks of plain bouillon and glucose bouillon and tubes of agar and glucose agar, plates being made from the latter.

Because of the report made by Rabinowitch that he had obtained positive blood cultures in cases of typhus fever by the use of an aerobic method, his medium was tested. The results were negative in all the cases tested although some of these cases gave positive results with the anaerobic method.

Anaerobic Methods.—The first successful results were obtained in two cases of endemic, and one case of epidemic typhus fever by the use of the ascitic fluid-kidney tissue medium, layered with liquid petrolatum, as advocated by Dr. Noguchi for the cultivation of spirochetae. I am indebted to Dr. Noguchi for a demonstration of his methods. The method introduced by Liborius-Veillon proved to be more satisfactory,—modified in that serum-

glucose-agar, originally suggested by Libman as an optimum medium, was used instead of glucose agar.[1]

Serum Employed.—The sterility of the fluid must be ascertained before use, by thorough aerobic and anaerobic methods, such as will be described in the full publication. Studies must also be made to exclude hemoglobinophilic organisms.

DEVELOPMENT OF THE ORGANISM OBTAINED: SUBINOCULATIONS

Colonies of the organism appear in the tubes in from three to sixteen days. Negative tubes were observed twenty-one days. On development, the colonies are removed and inoculated on slants of one half per cent. glucose-serum-agar, the latter tubes then being inserted in Buchner tubes.

The colonies usually appear in the lower two or three centimeters of the tube, occasionally also higher, but never within three centimeters from the top of the medium. The colony first appears as a small opaque spot. As it grows larger a brownish area of precipitation[2] develops in the medium about it. By direct sunlight or incandescent electric light (frosted bulb) the colony itself appears round and opaque, varying in size from one to six millimeters in diameter (including the area of precipitation), the size of the colony depending on its stage of development. On cross section it is Y-shaped, brownish in appearance, and soft in consistency. The arms of the Y are fusiform.

MORPHOLOGY

The organism is a small pleomorphic Gram-positive bacillus, which is non-motile, non-encapsulated and not acid fast. Its length varies from 0.9 to 1.93 micra, its breadth being from one fifth to three fifths the length. Most of the organisms are straight, occasional ones are slightly curved. Coccoid forms also occur. The ends are rounded or slightly pointed. In smears

[1] The details of the method will be described in the full publication.

[2] This phenomenon, which is due to acid production, was first described by Libman in 1901, when he advised the use of media containing carbohydrates and sera (non-coagulated) for the growth of poorly growing organisms.

from solid media, the organisms lie end to end, side to side or at angles to one another, there being no definite arrangement. Degeneration and involution forms appear early. The organism produces no spores. Polar bodies are occasionally demonstrable either at one end of the bacillus or both.

CULTURAL CHARACTERISTICS

Besides the usual studies of cultures grown in Buchner tubes or in Novy jars, inoculations were made in a variety of media in long test tubes. A saline emulsion of the organism was inoculated in the following media:

Agar,
½ per cent. glucose agar,
2 per cent. glucose agar,
Sugar-free bouillon,
2 per cent. glucose bouillon.

These media were used alone; layered with liquid petrolatum, with the addition of kidney tissue; with ascitic fluid; with ascitic fluid and kidney tissue; and with ascitic fluid and kidney tissue layered with liquid petrolatum.

There was no growth in the agar or sugar-free bouillon after twenty days observation. Growth was present in one half per cent. glucose-agar with ascitic fluid and kidney tissue, but was better in two per cent. glucose-agar. There is a minute flocculent growth at the bottom of the glucose-bouillon tube after eight days.

In Buchner tubes, after three days, on glucose-serum-agar there is a creamy white growth which does not spread and which in older cultures may become light brown in color. There is moderate precipitation which increases after three days and increases on subculture.

On potato, after four days there is a practically invisible whitish growth demonstrable by scraping the medium. On gelatin, fifteen per cent., there is no growth even in the thermostat. On litmus milk, there is a slight amount of acidity after eighteen days. On Loeffler medium, there is very slight growth.

The organism from both the epidemic and endemic cases was found to produce acid and precipitation in glucose, maltose, galactose and inulin and not in raffinose, mannite, arabinose, saccharose, dextrin and lactose. The thermal death point was found to be 55° C. for ten minutes. The organism was found to be non-filterable.

On plates, colonies could be developed only in glucose-serum-agar, appearing after seven days. Surface colonies were obtained only once. The deep colonies varied in size from pinpoint to one millimeter. They were round, oval or triangular, the last type predominating. Microscopically, the colonies were triangular or acorn-shaped, sharply circumscribed with irregular contour.

Aerobic Studies.—The organism is an obligatory anaerobe. It was at first thought that slight growth had occurred aerobically, after anaerobic cultivation. The strains were inoculated on a variety of aerobic media, with negative results.

GENERAL RESULTS OF THE BLOOD CULTURE STUDIES

Blood cultures were taken in seven cases of epidemic typhus fever during the febrile stage and the bacillus isolated in each.[1] From an eighth case blood was inoculated intraperitoneally into two guinea-pigs which developed the typical febrile reaction and from the blood of which at the height of the reaction the organism was obtained.

Blood cultures were taken in thirty-four endemic cases up to the time of crisis. Eighteen of these, or fifty-three per cent., yielded the bacillus.

Blood cultures were taken after the crisis in six of the cases of epidemic typhus fever and all proved negative. In three of these the organisms had been recovered during the febrile period of the disease. Nine of the endemic cases were cultured after the crisis and the bacillus was found in one of them twelve, and in the other, thirty-six hours after the crisis.

With the identical technic used for isolating the bacillus in typhus fever, anaerobic blood cultures were taken on one hundred

[1] In the full paper these facts will be elucidated by tables giving all the details.

and ninety-eight control cases and in no instance was an organism recovered which in any way resembled the bacillus recovered from cases of typhus fever.

THE IDENTITY OF THE ORGANISMS ISOLATED FROM VARIOUS SOURCES

The organisms isolated from the endemic typhus cases were found to be culturally identical with those isolated from the epidemic typhus cases. Not the slightest variation was found. The organisms isolated from guinea-pigs and monkeys in which the disease had been produced experimentally were also exactly the same.

A careful study of the facts in the tables brought out the interesting observation that the organism occurs more abundantly in the blood on the fourth and fifth days before the crisis than later. It was also found that the bacillus was found eighteen times as abundantly in the blood of the epidemic as in the blood of the endemic cases. Without laying too much stress on this exact figure, it is very evident that the bacteriemia is more intense in the epidemic than in the endemic cases. The two cases of epidemic typhus fever which had the most marked bacteriemia proved fatal.

Because of the late maturation of the colonies, the results of the blood cultures are usually only known after the termination of the illness and therefore can be used only for confirming a previously made diagnosis, but in two instances of supposed influenza, the organism was found after the crisis and then a careful investigation revealed the fact that both of the individuals had passed through an attack of typical typhus fever.

CONCLUSIONS

Attention has been drawn to the fact that the virus of typhus fever circulates in the blood of an infected person or animal, that the virus is not filterable and, therefore, of microscopic size; and that aerobic cultures made with a great variety of media are negative. Hence it was considered plausible that the infective

agent is an anaerobic organism. By means of an anaerobic method of blood culture a bacillus was isolated in pure culture from seven cases of European epidemic typhus fever, or one hundred per cent. of the cases studied during the febrile period. With the same method the identical organism was recovered during the febrile period of the local endemic form of the disease, in eighteen of thirty-four cases, or fifty-three per cent., and in two additional cases taken after the crisis. Similar blood cultures made in one hundred and ninety-eight control cases yielded no such organism.

Considered in conjunction with the serological and experimental evidence which follows, these facts prove that this bacillus is the etiological factor in typhus exanthematicus.

Following a very kind suggestion of Professor William H. Welch, it has been deemed advisable to name the organism, *Bacillus typhi-exanthematici.*[1]

THE ETIOLOGY OF TYPHUS EXANTHEMATICUS

II. SEROLOGICAL STUDIES[1]

PETER K. OLITSKY, M.D.

Abstract[2]

I. COMPLEMENT FIXATION DURING THE COURSE OF TYPHUS FEVER

In the beginning three antigens were used, one made up of the epidemic typhus organisms, one of the organisms of endemic cases, and a third of a mixture of both organisms. Later it was

[1] The name *Bacillus typhi exanthematici* was applied by Klebs in 1881 to a hypothetical organism in typhus fever. The name was never actually used, as the search for the organism proved futile. The hyphenating of "typhi" and "exanthematici" succeeds in giving us a binomial designation properly descriptive.

[1] This work was done under the tenure of the Eugene Meyer, Jr., Fellowship.

[2] A complete report will be published shortly in *The Journal of Infectious Diseases.*

found better to use an antigen made up of both strains of the typhus bacillus. The results were then found to be more uniform, and positive reactions more common.

Eleven cases of epidemic and thirty-four of endemic typhus fever were tested. Of twenty-five cases studied at the height of the disease, only two were positive, one giving a ++ reaction, the other a ++++ reaction. Both were tested one day before the crisis. The latter had a negative, the former a positive blood culture. Ten cases were tested at the crisis. Of these, two gave ++++ reactions, one a +++, one a ++, and the rest were negative. In the post critical stage of the disease, nine epidemic and thirty endemic cases were studied. Of these, 71.8 per cent. gave positive reactions.

The complement fixing antibodies reach their maximum concentration between the second and twelfth day after the crisis. Their persistence was studied in two cases, in one of which the reaction became negative between the sixty-fourth and the one hundred and thirteenth day after the crisis, and in the other case between the third and thirty-ninth day after the crisis. One may trace the development in an individual case of a negative reaction at the height of the disease to a ++++ reaction after the crisis.

One hundred and four control cases were studied with negative results.

Complement Fixation on Typhus Fever Cases with other than Typhus Antigens.—These antigens were made of *Bacterium coli, Staphylococcus aureus, gonococcus, streptococcus* (single antigens made of various types) and some Gram-positive anaerobic bacilli, having a morphology similar to that of the typhus bacillus (*Bacillus acnes* and bacilli isolated from ascitic fluid and from rabbit's kidney). These antigens were prepared in the same manner as the typhus antigen.

2. AGGLUTINATION REACTIONS DURING THE COURSE OF TYPHUS FEVER

Microscopical reactions were found to be better than macroscopical. Comparative experiments demonstrated that an epi-

demic typhus agglutinogen gave clumping with serum from endemic as well as from epidemic typhus fever, and an endemic typhus agglutinogen likewise gave positive agglutination with serum from patients suffering from either form of the disease.

In applying a mixed agglutinogen, positive agglutinations were obtained in more instances than positive complement fixation tests. For reasons which we will give later, only reactions in dilutions of 1 to 50 or higher were considered positive.

In forty-three cases of typhus fever during some period in the disease, thirty-nine, or 90.8 per cent., were found positive. Of twenty-four cases tested all were negative, except two which were tested a day before the crisis; both had a titer of 1 to 100. Of ten cases tested on the day of crisis, three were positive and seven were negative. In the apyrexial period, thirty-eight cases were studied of which only three were negative and 92.1 per cent. positive. The agglutinins evidently follow a curve similar to that of the complement fixing antibodies, the maximum concentration developing about four days after the crisis. The agglutinins have been demonstrated as late as five months after the crisis.

Agglutination Tests on Control Cases.—There were ninety-six control cases studied at various periods. Seven of these gave an agglutination in dilution of 1 to 20, but not in high dilutions. Of the seven cases one was a brain tumor; two, valvular defects; two, general paresis; one, carcinoma of the tonsil; and one, a case of alcoholism. The complement fixation in all these cases gave a negative result. It is because of the results in these cases that we regarded only such results as positive that gave agglutination in dilutions of 1 to 50 or higher.

There were three control cases in which the occurrence of a previous attack of typhus fever could not be excluded, in which reactions were found in dilutions of 1 to 100 to 1 to 200.

Agglutination with other than Typhus Organisms.—We endeavored to use as an agglutinogen all such bacteria as we were able to obtain in cases other than typhus fever, which showed any resemblance, morphologically, to the typhus bacillus, including the *Bacilus acnes*. In all such instances, when the agglutinogen

was mixed with convalescent typhus serum, the results were negative.

3. PRECIPITATION REACTIONS IN TYPHUS FEVER

Of ten cases studied at the height of the disease all were negative. Of three cases tested at the crisis, one showed distinct clouding in 1 to 1,000 dilution. Fourteen, or 73.6 per cent. of nineteen cases tested in the fever-free period, gave precipitations. Three of these reacted in dilutions of 1 to 1,500; four in dilutions of 1 to 1,000, while the rest showed precipitates in dilutions of 1 to 100.

With each test a negative serum was included. Such control cases always gave negative reactions. The precipitin formation is evidently absent at the height of the disease but becomes in evidence at the crisis and proceeds to increase until well along in the post critical stage.

4. BACTERIOTROPINS

While discrepancies are common in making such studies, the average results demonstrate that the opsonic index increases at the crisis and remains high in the convalescent stage of the disease. Similar rises were noted in artificially immunized serum (rabbit). The probability is that this method is one of the most potent on the part of the patient in overcoming the infection. We noted during these examinations that phagocytized bacteria had a marked tendency to become fragmented and take the stain very lightly. Lysis of the typhus bacilli apparently is very active within polymorphonuclear cells of typhus immune subjects.

Other features of this work, the occurrence of allergic reactions, and the nature of the toxin produced, will be reported later.

5. THE IDENTITY OF THE ORGANISM ISOLATED FROM CASES OF ENDEMIC TYPHUS FEVER TO THAT ISOLATED FROM CASES OF EPIDEMIC TYPHUS FEVER

For the purpose of investigating this subject, cross fixation investigations were made both in artificially produced immune

serum as well as in natural immune serum and similarly by cross agglutination tests. From studies of rabbit's immune sera the conclusion is definite that from a serological viewpoint the organism obtained from epidemic and the one from endemic typhus fever are two strains of the same bacterium.[1]

6. SEROLOGICAL STUDIES IN ANIMALS

Monkeys.—Of six monkeys that reacted to the typhus virus, complement fixation and agglutination tests were positive in five, or 83.3 per cent. These reactions were still positive twenty days after the crisis.

As the agglutination (Widal) reaction in typhoid fever is no absolute sign of protection from that disease, so in typhus fever, the serological manifestations of complement fixation and agglutination, while often appearing in connection with immunity, are no indications of immunity. The four monkeys mentioned above, two with reactions and two without, were injected with active typhus virus. Three of the monkeys reacted, one did not.[2]

We shall report in the future our results in prophylactic vaccination against typhus fever, a work which is now in progress.

Guinea pigs.—Although these animals were proved to be immune after reacting to typhus virus, the serum contained no agglutinin or complement fixing bodies. It is most probable that this animal develops its high grade of immunity by means of its tissue elements and only to a very slight degree by means of the circulating blood.

There is a possibility that bacteriotropins may exert a great influence in these animals and likewise add to the factors of the cellular immunity which may be present.

Rabbits.—Rabbits are not susceptible to the typhus bacillus in small amounts. When small yet increasing amounts of bacteria are given, they develop very potent immune serum.

[1] See tables in full publication.

[2] The production of complement fixing bodies as well as agglutinins in monkeys can be paralleled in man.

CONCLUSIONS

A careful examination of the above results leads one to the belief that there is most intimate relationship between the typhus bacillus and typhus fever. All the serological reactions occurred in orderly manner, usually becoming demonstrable at the time of the crisis and increasing in concentration after the crisis. There is but one conclusion possible: Typhus fever is a reaction against the organism which has been isolated by Dr. Plotz. The presence of the reactions does not indicate absolute immunity.

As regards the relationship of the occurrence of the reactions to the results of the blood cultures, these facts are noted:

There were sixteen cases in which the blood culture was taken at the height of the disease and in which bacteria were not found. By examining the table which is included in the full publication, it will be seen that most of our strongest serological reactions occurred in just such cases.

THE ETIOLOGY OF TYPHUS EXANTHEMATICUS

III. EXPERIMENTAL STUDIES[1]

GEORGE BAEHR, M.D., HARRY PLOTZ, M.D., AND
PETER K. OLITSKY, M.D.

Abstract[2]

For the purpose of ascertaining whether the organism recovered from the blood of typhus fever patients was also found in animals having experimental typhus fever, a series of twenty-four guinea pigs was inoculated with defibrinated blood obtained from patients or animals with the disease. Blood for cultures was obtained by direct aspiration of the heart sometime after the

[1] This work was done under the tenure of the Eugene Meyer, Jr., and Moses Heineman Fellowships in Pathology.

[2] A complete report will be published shortly in *The Journal of Infectious Diseases.*

onset of the fever. From eight, or thirty-three and one third per cent. of the guinea pigs in this series, the same bacillus was isolated from the blood as had been obtained from the blood of individuals with typhus fever. The percentage of positive blood cultures is less than that obtained in human cases because we were forced to use very small quantities of blood for the cultures, the average amount being three cubic centimeters.

In the positive blood cultures the colonies averaged about one per cubic centimeter of blood. This is more than was found in the patients with endemic typhus fever, but less than in individuals with epidemic typhus.

In only one of nine guinea pigs having mild febrile reactions was the blood culture positive. In fifteen animals with severe reactions the blood culture was positive in seven. This relationship between the blood culture results and the severity of the disease was also observed in human typhus cases.

A majority of the blood cultures were positive when taken between twenty-four and seventy-two hours after the onset of the fever. This observation assumes especial interest when the temperature curves of thirty-five other animals which were permitted to live for the entire course of their disease are analyzed. In the majority of instances (sixty-six per cent.) the fever reached its highest point on the second or third day of the disease, in other words between twenty-four to seventy-two hours after the onset. This is the period when the blood culture is most frequently positive in the infected animals.

Two strains of bacilli obtained from two of the epidemic typhus cases (epidemic cases 1 and 5) were inoculated intraperitoneally into guinea pigs. During the first twenty-four hours after the inoculation both animals developed a slight transient elevation in temperature, after which it remained normal for six and eighteen days respectively. The temperature then rose suddenly to 104° F. (40° C.) at which level it continued. One animal lived during the entire course of the disease, the fever lasting six days and ending abruptly. On the third day of the disease in the other guinea pig a blood culture was made. Seven days later a charac-

teristic colony appeared in one of the culture tubes. This organism upon subculture proved to be both morphologically and culturally identical with *Bacillus typhi-exanthematici.*

Other guinea pigs and monkeys were subsequently inoculated with the two strains of bacilli used in the above experiments or with strains from three other epidemic cases after they had been on artificial media (glucose-serum-agar) for more than three or four weeks, and all strains were then found to have completely lost their virulence. In each instance the inoculation was followed by only a slight transitory rise in temperature during the first thirty-six hours, a reaction also observed in the experiments with virulent organisms and apparently due to a toxin action. After cultivation on artificial media for more than a month, all strains of epidemic organisms also lost this toxin action.

This rapid loss of virulence explains why the reproduction of typhus fever in animals by inoculation of the bacilli was not done more extensively. The positive blood cultures in cases of epidemic typhus fever were obtained at the very beginning of the work. Subsequently when the importance of inoculating the organisms into animals within the shortest possible time after isolation was realized, no more cases of epidemic typhus fever were available.

We hope to have the opportunity very shortly to amplify this phase of the work. It is important, however, that we have demonstrated that with bacilli recently isolated from epidemic cases of typhus fever the disease can be reproduced in animals and that at the height of disease so produced the identical organism can again be recovered from the blood.

Experiments carried out with six strains of bacilli from the endemic cases (endemic cases 1, 2, 18, 23, 27 and 40) and with those isolated from three animals (guinea pigs 21, 24 and 103) with typhus fever, revealed the fact that they lost their virulence outside the body still more rapidly than did the epidemic typhus strains. Before sufficient growth could be obtained for inoculation, the organisms were on artificial media for two to three weeks, or even longer. When finally ready for inoculation such

organisms were not only avirulent, but they did not even possess the power of producing toxic rise in temperature after inoculation, a property only lost by the epidemic typhus organisms after cultivation for over a month.

Both morphologically and culturally the organisms isolated from the epidemic and the endemic type of the disease proved to be identical, and both were found to possess the same specific antigenic properties. This variation in virulence and in toxin production is the only essential difference which we have been able to demonstrate between the organisms derived from the two sources. Its importance lies in that it supplies us with a possible reason for the difference in the degree of bacteriemia and in the severity of the two diseases.

RELATION BETWEEN THE NUMBER OF BACILLI IN TYPHUS BLOOD TO ITS INFECTIVITY

The observations presented thus far in this paper have demonstrated the association of the bacillus recovered from cases of typhus fever with the disease as reproduced in the experimental animals. Further evidence from the experimental standpoint that this organism is the etiological agent in typhus fever was readily obtained by a study of the relation between the number of the bacilli in typhus blood and its infectivity.

A calculation of the average amount of organisms apparently contained in the quantity of blood inoculated into each animal was estimated from the total number of colonies which developed in the blood culture tubes.[1]

The uniformity of the observations on this series of fifty-one animals clearly indicates that typhus blood which contains no bacilli, or only very few bacilli, is *not* infective for animals. Typhus blood in which the bacilli are more numerous is infective. These experiments therefore demonstrated that infectivity is absolutely dependent upon the presence of a sufficient number of

[1] The tabulation of these results and the protocols of the experiments upon which these conclusions are based will be found in the complete paper in *The Journal of Infectious Diseases.*

these bacilli. This in itself is conclusive evidence of their etiological significance.

A study of the serum of individuals who have been exposed to infection by contact with human beings or animals suffering from typhus fever, led to the interesting observation that some of these people develop positive complement fixation and agglutination reactions without having had any clinical evidences of the disease.

CONCLUSIONS

It has been shown that a bacillus, identical with that recovered from patients with typhus fever, can also be isolated from the blood of animals in which the disease has been reproduced by inoculation of typhus blood. In such animals, the frequency of the bacilli in the blood is directly proportional to the severity of the illness. In individual animals it is greatest at the height of the disease.

It has also been shown that with the bacilli isolated from epidemic cases of typhus fever, it is possible to reproduce the disease in animals. And furthermore, at the height of the disease in such animals, the identical organism can be recovered from the circulating blood.

Finally, it has been shown that typhus blood is only infective if it contains a sufficient number of these bacilli.

From these observations and the results of the bacteriological and serological studies, we believe ourselves justified in concluding that this bacterium is the causative agent in typhus exanthematicus.

Discussion of papers by Dr. Plotz, Dr. Olitsky, and Drs. Baehr, Plotz and Olitsky:

DR. NOGUCHI: I am very fortunate indeed to have the opportunity of hearing and discussing the important papers just presented by Drs. Plotz, Olitsky and Baehr this evening, as I had the great privilege of being shown the organism by Dr. Plotz when he first isolated it from typhus cases about a year ago. At that stage of the investigation it was of course too early to form any definite opinion as to the etiological relationship between the organism and the disease in question, but now that further evidences that are required for settling such a problem are brought out in a most strictly scientific and thorough manner, it must be evident to anyone that the causative organism of this mysterious disease has been at last discovered. I was interested to hear that not all ascitic media could be used for the first isola-

tion of the typhus organism, as this agrees with my own experience with the cultivation of spirochætes, poliomyelitic microörganism, rabies virus, etc. The question of active and passive immunity, as well as the distribution of the organism within and without the body of the infected host, will undoubtedly be soon solved. I wish to congratulate Dr. Plotz, Dr. Olitsky and Dr. Baehr for this splendid contribution to the study of communicable diseases.

DR. PARK: When Dr. Plotz first announced his discovery many of us were somewhat skeptical, as it seemed an accident. But to-night it is plain that this investigation of the disease was carefully planned and the discovery was after much preliminary work. Dr. Noguchi's previous studies on anaerobic cultures led up to it. I see very few points that have been left unfinished in the work, but there are two points apparently not brought out which are fundamental. There may not have been time to take them up yet. Is the freshly isolated culture virulent for other animals than the guinea pig and monkey? I think Dr. Baehr said that in rabbits large amounts would cause infection, but are other animals similarly susceptible? Secondly, are the monkey and guinea pig, which have been infected by the fresh cultures and recovered from the attack, immune to the blood from a case of typhus fever in man or monkey at the height of the infection? If these two questions can be answered satisfactorily there is no other evidence required. The work appears to have been splendidly done.

DR. N. E. BRILL: These most brilliant papers afford me in particular the greatest satisfaction, because they settle in my mind that the etiology of typhus fever is at last discovered; because they offer for the first time the absolute proof that the disease described by me, which I was the first to assert might be an attenuated form of typhus fever and which I have always believed was related to typhus fever, ever since the important experimental studies on the cross immunity of these two types of fever, is due to the same organism as is epidemic typhus, and hence that they are identical as Anderson and Goldberger asserted; and because the infective agent just revealed may afford a rational means for prophylaxis and perhaps for the cure of typhus fever. We must accept from the work which has been communicated to us to-night that typhus fever exists clinically in two forms, one the classical, epidemic and virulent variety, and the other the mild, attenuated form to which I had the honor of calling the attention of physicians and which exists continually in New York City and in other cities of the United States. Up to this evening, while I had admitted the relationship of these two forms, I could not agree with the deductions of Anderson and Goldberger which they drew from their experimental work, viz., that their work proved the absolute identity of typhus fever and so-called Brill's disease. The reasons, which they urged justified their conclusion, were that when an animal was infected with Brill's disease it was subsequently immune to infection with typhus blood, and on the other hand that when an animal was infected with typhus fever it became immune to infection by the virus of Brill's disease. In the discussion of this feature of their work presented by me at the meeting of the International Medical Congress held in London in 1913, I presented the following arguments against this reasoning: When an individual is infected

by vaccinia, he is for a time immune to small-pox, and on the other hand an individual infected by small-pox is subsequently for a time immune to infection by vaccinia. Are small-pox and vaccinia therefore identical diseases? We will all most likely admit that these two diseases are related but not identical. Again, Metchnikoff and Besredka have shown in their very pretty work on immunity in typhoid fever, that when a monkey is once infected by paratyphoid fever, such monkey is immune to typhoid fever; yet paratyphoid and typhoid are related but not identical diseases. Above all I insisted that it was not justifiable to speak with positiveness on the identity of two diseases, especially when the causative organism which most likely produced the diseases under discussion were absolutely unknown.

I should like to say a few words on the subject of the transmission of typhus fever, though it is hardly possible in the five minutes allowed me by the chairman to discuss any of the many interesting subjects suggested by the papers of the evening. Therefore I may only hint at this subject. Nicolle was the first to show that a monkey could be infected experimentally with typhus fever by means of the bites of body lice which had been permitted to feed on a typhus fever subject. Ever since then it has been accepted that typhus fever is transmitted by the agency of the body louse. Anderson and Goldberger not only confirmed this observation but showed that the same results occurred when head lice were used as the agents of transmission. It is very likely that the epidemic form of typhus fever is spread in this way. It would appear from our own observations that this means of transmission is not important in the mild or endemic form of the disease, and that there is most probably some other mode of transmission. These observations are as follows: As was shown by Nicolle, the body louse cannot live at higher temperatures than 12° to 14° C.; it thrives only in the cold when it is most active and presumably most virulent. Anderson and Goldberger showed that when lice were collected and kept in a test-tube in the pocket of the experimenter they died even at such a moderate degree of warmth. It is true that epidemic typhus occurs most frequently in the colder months, as anybody may see who consults the statistics of Murchison, who states that out of 18,230 cases of epidemic typhus fever observed in the London Fever Hospital between the years 1847 to 1870, only 3,730 occurred in the warm months of the year; that July and August furnished by far the least of these. In other words, only about one fifth of typhus fever cases appeared in the summer months. Contrary to the seasonal preference observed in the epidemic variety, the form of the disease which the authors have called the endemic form, shows that by far the largest number of cases occur just in the hottest months of the year, months in which the body louse is not at all active. All my papers show this feature; in fact in the last reported series at the International Congress, of 62 cases reported in 1911 and 1912, 42 occurred in the warm months; 28 of these appeared in the months of July, August and September. The warm months from June to November in our cases furnished twice as many cases as all the rest of the year. Again, if the body louse or even the head louse were the infecting agent in the mild form of the disease, how is it that no family infection appears, that the husband is most rarely

infected by the wife, or the wife very rarely by the husband? In over 400 cases of this form of the disease, there has been only one case in which the husband and wife were infected, one by the other. This is a feature which it seems to me requires further study and investigation, for it seems likely that there is some other means of transmission than by the vermin just accused. Finally before I sit down I want to pay my tribute of congratulations to the authors of this evening's epoch-making work in our knowledge of typhus fever.

DR. MELTZER: I cannot add anything of value to the discussion. I am not a bacteriologist and feel that I am not entitled to offer a statement to the effect that the three communications offered to us prove conclusively that the organism discovered by Dr. Plotz is the real cause of typhus, endemic or epidemic. But since you called upon me, Mr. Chairman, to add something to the discussion, I gladly say this: It gave me great pleasure to listen to the way, the scientific manner and the thoroughness in which these investigations were carried out, and that I greatly appreciate the scholarly and lucid manner in which the results were presented to us. We may congratulate ourselves on the accession to our ranks of this group of young investigators.

DR. FRIEDMAN: I understand that this is not a clinical evening, but a discussion of the origin of typhus. Five years ago I took part in a discussion of Dr. Brill's paper and I must say that I was the first one to state definitely that the symptom complex he described was nothing else but typhus. Hardly anyone then wanted to agree with me. They said they had observed these cases for fourteen years and they were not typhus. Dr. Warren Coleman alone, in a personal communication, said he thought the disease might be a form of typhus. I do not minimize Dr. Brill's work. Men who should know more about typhus than Dr. Brill have made mistakes. In Manchuria, a St. Petersburg professor, Dr. Botkin, found a deviation in type and described it as a different disease. It was clear to me without any bacteriological evidence that Dr. Brill's cases were not different from typhus. In regard to the louse, a Russian physician inoculated himself with the blood of a typhus patient and eighteen days later developed the disease. This inoculation from man to man shows that typhus transmission can occur without the body louse. But I believe the body louse increases the virulence of the disease. This is seen in Russian prisons. Everyone may get typhus from one case, the prisons being filled with lice, and I believe the infection derived through lice is more severe.

DR. LOURIA: There is nothing for me to add. From the clinical viewpoint I have to recall cases of typhus fever which I observed in my student days. It is a common disease in Russia. I saw it constantly in my early student and hospital days. When my attention was called to the work of Dr. Brill I was impressed with the fact that these cases looked like what I had seen, but with differences; that is, they run a mild course. Although these two types have been proven bacteriologically and experimentally identical, yet I feel there must still be something missing in the work. I feel, however, that the answers will be presented in time by these able workers.

DR. MANDLEBAUM: I should like to draw attention to the great importance of Dr. Brill's work on the isolation of cases of endemic typhus fever—so-called "Brill's disease"—from other fevers. Were it not for his work and the observations that followed, the identity of "Brill's disease" to typhus fever would not likely have been made, and the epidemic cases which were held at quarantine would surely not have been investigated in connection with this work.

When the cause of an acute infectious disease is discovered, one naturally looks for some serum or vaccine for the treatment, or, what is more important, for its prevention. We have heard an allusion made to a prophylactic vaccine. I think I may be permitted to state here that some members of the commission who have already gone to Serbia, and others who intend to go, have been injected at their own request with the vaccine made by us, without any guarantee, of course, as to its efficacy. The efficacy of any vaccine, as we all know, can only be determined when employed in an epidemic.

DR. LIBMAN: In regard to the question of secondary invaders,—the suggestion has been made that the bacillus described to-night may be an analagous finding to that made in yellow fever by Sanarelli. The latter studies were mostly made after death and in the main mixed cultures were obtained. The work in typhus fever was all done *intra vitam* and the organism was always obtained pure. The serological studies also prove the relationship of the bacillus to typhus fever. If this organism were not accepted it could be only as the basis that there were two etiological agents,—an assumption not warranted by experience.

The organisms when isolated may have lost their virulence because of their long stay in sugar media. If even without sugar they should be proven non-virulent we might make the assumption that the louse is of importance for maintenance and development of virulence.

As to Dr. Brill's remarks on the question of transmission,—either endemic typhus is not conveyed exclusively by lice or we do not yet understand all the features of louse transmission.

The discovery of Dr. Plotz did not depend on chance observation. I have been informed that he had the problem of Brill's disease in his mind when he was a medical student, and that he entered the laboratories of the Mount Sinai Hospital to work on the etiology of the disease. The organism was obtained the first time he tried good methods for it, which is unusual. When he showed me the organism I believed that he had found something of importance and advised him to go on. I consider it a privilege to have been associated with Drs. Plotz, Olitsky and Baehr in the work, although I consider myself more in the character of a watchman than anything else.

DR. BAEHR: Dr. Libman has answered most of the questions. In reply to Dr. Park, we wish to say that we have tested the susceptibility of other laboratory animals, such as rats, mice and rabbits and some observers have tested cats, dogs, sheep and goats. No other animals except monkeys and

guinea pigs respond actively to the inoculation of a typhus virus. In reply to Dr. Brill as to the possibility of transmission of the endemic disease by other insects than the body louse,—we prefer not to commit ourselves at present. There may be another agent. Thus far it has only been possible to demonstrate transmission by means of the body louse, and the presence of the latter upon many of the endemic cases of typhus fever, even at the time of their reception in the hospital, is therefore very significant.

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CONTENTS

DR. HANS ZINSSER, *President.*

FOREIGN BODIES IN GIANT CELLS[1]

F. C. WOOD, M.D.

(From St. Luke's Hospital, Pathological Department, F. C. Wood, Director)

The patient from whom the material to be shown was removed was a woman (C. B., St. Luke's Path. No. 11022), twenty-six years of age, who about a year previous had had a paraffin injection in the neck for cosmetic purposes. Owing to the considerable hyperplasia which resulted from the injection, it was necessary to remove the mass surgically.

The tissues showed the usual morphological appearance found after such injections, consisting in a very considerable inflammatory reaction of a chronic nature with many lymphocytes

[1] Read at the March meeting of the Society.

and plasma cells lying in a meshwork of granulation tissue. Scattered throughout this granulation tissue were numerous giant cells, some surrounding globules of the paraffin, and others not showing any included structure, while a considerable proportion contained stellate bodies which occupied the center of the cells. These bodies consisted of a central mass, 2 to 3 μ in diameter, from which sprang curved spicules, fifteen to twenty in number. The diameter of the whole body was 20 to 25 μ. These bodies stained fairly well with hematoxylin and somewhat more deeply with Weigert's elastic tissue stain. In the writer's opinion, they probably represent condensed protoplasmic shells about crystals of paraffin, or possibly fatty acids. Mallory and others consider that they are fibrinoid in nature.

The literature concerning these structures, which have, of course, only an academic interest, is not very extensive. The first report was that of Ris, who described similar giant cells in an omental cyst removed from the peritoneal cavity of a man, fifty-one years old. The cyst was about 7 cm. in diameter, with a wall 4 mm. in thickness. The lining of the cyst was composed of granulation tissue with many cholesterin crystal giant cells and also giant cells containing the peculiar stellate structures under discussion. Ribbert, who saw the preparations, thought that they were imperfectly developed portions of moulds (*Schimmelpilze*). These stellate bodies did not stain with the ordinary nuclear stains nor with Weigert's fibrin stain. They measured about 15 to 25 μ in diameter and were composed of curved needles radiating from a central homogeneous area. About one-third of the giant cells contained these bodies.

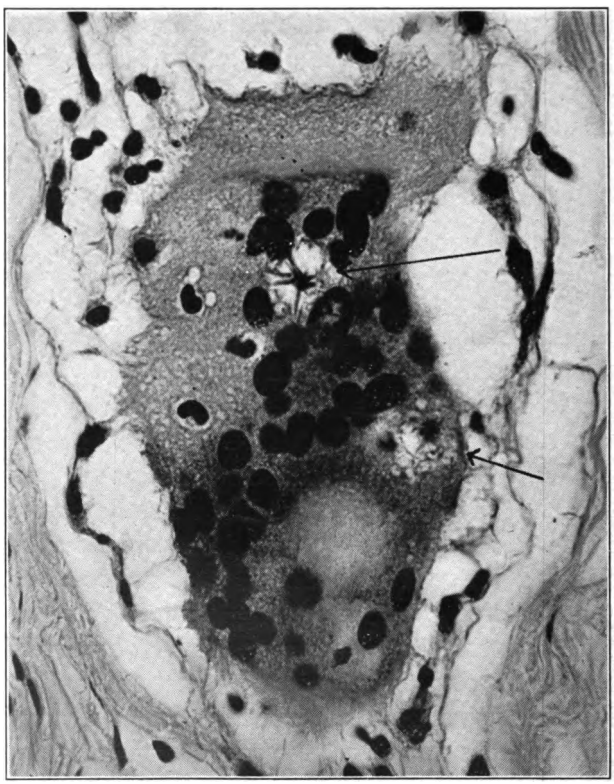
The next report was that of Wolbach, who stated that in 900 autopsies he had found five cases in which giant cells contained small radiating inclusions. In the first case the structures were present in the lungs; in the second, in the lymph nodes; in the third, in the lungs and lymph nodes; in the fourth, in the spleen, liver, and lymph nodes; and in the fifth, in the lung, spleen, and liver. In one case they were found in the peripheral sinuses of the lymph nodes. The smaller forms were often included in endothelial leucocytes and occasionally within endothelial cells which

were attached to the walls of the lymph spaces. Wolbach called attention to the fact that these inclusions were not parasites though they resembled structures occasionally encountered in experimental lesions produced by certain fungi. He held that it was impossible that they should be artefacts. For the material which he studied the best stain was found to be Mallory's phosphotungstic acid hematein; Gram's stain colored the central body and the spines a deep blue, the intervening material taking the counterstain; and with Mallory's eosin-methylene blue the spines and central body were stained a deep purple and the intervening portion a pink color. The bodies were not soluble in caustic potash or in hydrochloric acid, and were not stained by silver nitrate in frozen sections of formalin material. Scharlach R and osmic acid did not stain them nor did iron hematoxylin or Weigert's elastic tissue stain. The iron reaction was negative.

Vogel described similar bodies in giant cells in a case of obliterative capillary bronchitis in a child eleven years old. The giant cells were found in the connective tissue replacing the bronchi and the perivascular connective tissue. They contained one to three star-like bodies which suggested crystals; took a rather faint stain with hematoxylin, and colored best with Weigert's stain for elastic fibers. Fat, fatty acids, and iron could not be demonstrated in the giant cells. Vogel thought that these bodies were probably not altered elastic tissue, but he could give no suggestion as to their nature. He referred to articles by Ssudakewitsch and Rona, but the structures figured by these two authors do not in the least resemble the stellate bodies under discussion.

Iwanzoff found similar structures in a myomatous uterus removed from a woman, fifty years old. In this myoma, which showed a considerable amount of hyaline degeneration, there were areas of lymphoid infiltration containing irregular giant cells. In some cases these giant cells were so abundant that they formed a large part of the nodule. There was nothing peculiar about the giant cells, except that when stained with Weigert's elastic stain they showed peculiar radiating structures previously described by Wolbach. They were not bacterial in nature and did not stain except with Weigert's stain. The writer discusses

the question of whether these are phagocyted elastic tissue fibers, such as are frequently seen in tuberculosis of the skin, whether they are parasitic inclusions, or whether they are astrospheres. He referred to a paper by Wakabayashi in which the astrospheres in tuberculous and other giant cells are described, and thought



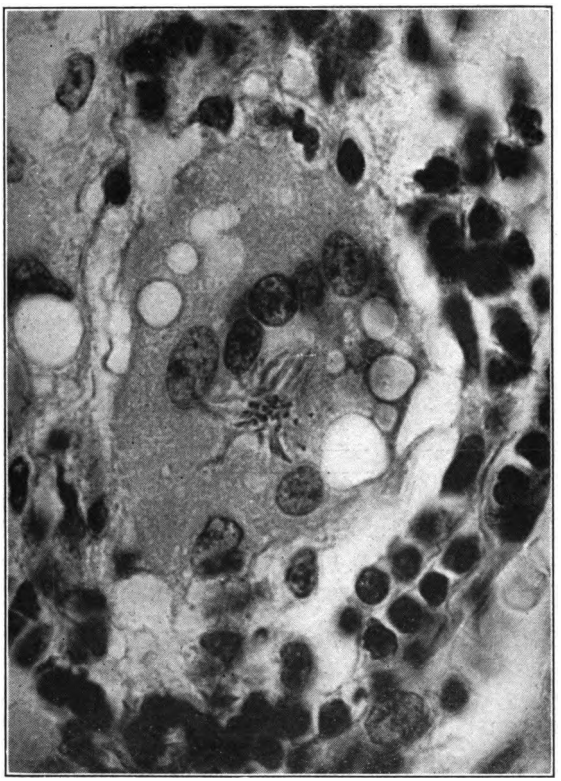
Stellate Bodies in Giant Cells. × 750.

that these bodies closely resembled the structures which he had reported.

Mallory in his text-book shows a giant cell (Fig. 120, page 207) from a case of leprosy, which contains a spiculated body of the type under discussion. He gives no details except the legend under the cut. In another cut he shows similar spiculated bodies

(Fig. 465, page 613), the text referring to these reading as follows:

"Spiculated bodies have been found in the spleen in a few instances inclosed in endothelial leukocytes and giant-cells. They may be quite numerous and occur in foci or diffusely scattered.



Stellate Bodies in Giant Cells. × 750.

The lesion resembles miliary tuberculosis, but no necrosis is produced. The bodies seem chemically to be of a fibrinoid character. They are evidently not the cause of the lesion, which is probably of infectious origin, but a secondary formation."

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Discussion:

DR. LARKIN: What relation do these bodies bear to the inclusion bodies in cancer?

DR. WOOD: They differ from degenerating cells in carcinoma that I have seen, and I suspect that they may be fatty acid crystals about which condensation of protoplasm has taken place. If they were cellular fragments they would, I think, be more often met with; on the contrary, these stellate bodies are very rare.

CONGENITAL SARCOMA OF VAGINA

A. B. EISENBREY, M.D.

(*From St. Luke's Hospital, Pathological Department, F. C. Wood, Director*)

In 1911, reports of one hundred and two cases of sarcoma of the vagina were collected by MacFarland of Philadelphia. Of these cases, thirty-four were of the type known as sarcoma botryoides, or grape-like sarcoma. All but one of these cases proved rapidly fatal. They occurred in young children from three months to five years of age. In one case the tumor was noticed at birth. It was shown to be essentially a disease of childhood. On account of the diversity of cell types found it was regarded by many as a congenital tumor.

The case I wish to report was three and one half years of age, a patient in St. Luke's Hospital, on the service of Dr. Abbe. One

year previously the family noticed that on crying or making efforts at stools a polypoid mass projected from the vagina. An operation was then performed and the child remained well for about a month, when there was a recurrence. Four operations were performed before her admission to St. Luke's Hospital in March, 1915, at which time the vaginal growth was again removed. While in many cases reported, the tumors were found to be single, the growth in this case was made up of multiple tumors, and involved the entire surface of the vaginal wall. There was apparently some growth also on the margin of the cervix. The child had marked difficulty in micturition and defecation. Palpation through the rectum revealed a sausage-like mass which filled and appeared to be confined to the vagina.

The specimens received for examination were six or eight rounded, pedunculated masses, resembling nasal polyps, pinkish in color, and quite oedematous. In some the pedicle was fibrous. All of the growths were covered by epithelium, which showed a few erosions. Two or three of the small masses consisted of vaginal mucosa containing areas of minute soft nodules beneath the epithelium. Microscopic sections showed a typical polyp-like structure, some of the denser areas consisting of closely packed spindle cells. A few areas of distinctly myxomatous type were found. The predominating cell was of the spindle type. Many young striated muscle fibers were present in some of the polypoid growths, quite apart from the blood vessel walls and the vaginal musculature. They occurred singly and in small bundles. It is on this finding that the "congenital" nature of the growth is based.

Discussion:

DR. LAMBERT: I am not at all familiar with the first type of sarcoma of the vagina. On the basis of the microscopic appearance I should hesitate to call it sarcoma. I should rather call it a benign "mixed" tumor or teratoma.

DR. EISENBREY: There were a great variety of cells described in connection with this type of tumor. The name was given on account of the grape-like nature of the growths. In some, the clusters seem definitely cystic. Some were myxomatous, but the predominating type of cell was the spindle variety; some showed round cells; some were combinations of the two; three cases were fibromatous in type, others fibromyxomatous; all of these

types, however, have been included under sarcoma botryoides. In a large number there were some muscle fibres and in some cartilage. MacFarland's own case did not contain muscle fibers; it was made up entirely of spindle cells, and areas of œdema and degeneration were numerous. They are certainly malignant growths.

DR. LEVIN: This tumor seems to be similar to the mixed tumors of the testicle where we find various kinds of cells. They are probably fœtal in origin.

DR. EISENBREY: That is the reason I classified this case as a "congenital" tumor.

XANTHOMATA OF TONGUE AND ELBOWS

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(*From St. Luke's Hospital, Pathological Department, F. C. Wood, Director*)

XANTHOMA OF TONGUE

The specimen was from a man thirty-five years of age, a heavy smoker, a patient in St. Luke's Hospital, on the service of Dr. Abbe, in October, 1914. Two months previously he noticed a hard, painless nodule about 0.6 cm. in diameter on the dorsal surface of the middle of the tongue, slightly to the right side. On section the growth showed distinct demarcation from the surrounding tissue. It was covered by epithelium, and was of firm consistency. Many cells could be scraped from the cut surface. It was whitish in color, and no yellow pigmentation was noticed. Microscopic sections showed groups of characteristic fat-containing cells lying in meshes of a rather dense connective tissue stroma. Under the polarizing microscope the fat proved to be of the double refractile variety.

XANTHOMA OF ELBOWS

These specimens were from a young Russian woman, twenty-six years of age, a patient in St. Luke's Hospital, on the service of Dr. Downes. Since childhood she had had yellowish lumps on her elbows. Two months before admission in February, 1915, she noticed the lumps on her elbows were becoming larger, and

that some small ones were beginning to appear on both knees. There was no history of previous illness, but the patient was quite neurotic in type, and had physical signs of incipient Graves' disease. Tumors removed from elbows at operation showed well encapsulated, bright yellow, fibrous nodules, which were not attached to the skin. The loose tissue about the nodules and the skin also showed a bright yellow color. Microscopic sections showed typical fat-containing cells lying in meshes of a rather dense fibrous stroma, and also a few fatty cells and fat masses that were loose in the tissue about the nodules. The fat was doubly refractile with the polarizing microscope. Many crystal spaces with giant cells about them were present in some of the dense portions of the nodules.

Discussion:

DR. PAPPENHEIMER: Are these spaces cholesterin crystals?

DR. EISENBREY: Yes. They were considered to be cholesterin and in the fresh state sheaves of fatty acid crystals also were found.

DR. LAMBERT: Isn't the tongue an unusual place for xanthoma?

DR. EISENBREY: Yes. It is generally found in the abdominal organs, the trachea and pericardium. The small xanthomata about the eyes that occur in old people are probably the result of degenerative processes and not neoplasms. The diagnosis in these cases was made on the nature of the fatty cells and the double refractile nature of the fat to polarized light.

DR. LAMBERT: In the second case, I should think there might be a question as to its being xanthoma; occasionally cells containing chlosterin esters are found in other growths. Was the cholesterin content of the blood determined in these cases? Contradictory results regarding this question have been reported. In a recent paper Rosenbloom (Arch. Int. Med., 1913, XII, 395) reported normal cholesterin content of the blood in a case presenting multiple xanthomata.

EOSINOPHILIC INFILTRATION OF THE PANCREAS

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The case which is the subject of this report possesses interest in that as far as can be ascertained, it is the only case on record which presents an eosinophilia limited to the pancreas alone and

existing in that organ without discoverable cause and independent of a generalized eosinophilia.

Before describing the histological characteristics of the organ involved, it may be well to consider briefly the cause of generalized and local eosinophilia. The main authority consulted is the exhaustive study on general and localized eosinophilia by E. Schwartz in the *Ergebnisse der allgemeine Pathologie,* 1914, Vol. 17, Part I.

General Eosinophilia: Drawing his facts from many sources, Schwartz places the normal limits of the eosinophilic cells in the circulating blood between 2 per cent. and 4 per cent. in adults, 2 per cent. and 5 per cent. in children. Race, sex, age, temperature of the environment, pregnancy and parturition seem to bear no direct influence upon the eosinophile cells. The condition of nourishment appears to exert some influence, starvation reducing the number of cells, which, however, rapidly returns to normal upon the restitution of sufficient nourishment.

Splenectomy or ligation of the splenic vessels is followed by an immediate decrease in the number of cells, then a rise to a supernormal figure and then a slow drop to a subnormal figure which is then maintained.

The effects of many and varied toxic agents have been studied. Those which produce an increase are antimony, CO, CO_2 and pilocarpine. Hæmotoxic substances seem to exert no constant effect upon the number of eosinophiles. Anaphylactic shock is regularly followed by a marked and protracted eosinophilia. This phenomenon is considered to be the explanation of the eosinophilia observed in asthma, hay-fever, many of the dermatoses and certain obscure intestinal phenomena which have been held by many to be due to localized anaphylactic conditions.

Disturbances of the glands of internal secretion do not seem to exert any constant effect upon the eosinophiles except in the thyroid; hypothyroidism being fairly constantly accompanied by an increase, hyperthyroidism by a decrease in the number of eosinophiles. Certain nervous diseases are accompanied by an eosinophilia, among which may be named epilepsy, especially in periods immediately following active seizures, dementia præcox, paranoia, and many psychoses of various origins.

The conditions which produce the most striking examples of eosinophilia are those associated with parasites. The site of the infection does not seem to influence the blood picture, for similar extreme examples are found in all of the groups of parasites whether they exist in the intestinal canal, the parenchymatous organs, the urinary system, the muscles, or the blood. They differ markedly in their eosinophilic properties, however, some of the parasites being unable to stir up any response, while others produce such a profound effect that the eosinophilic cell may occupy an almost exclusive position in the composition of the white elements of the blood. In general, higher values are observed in children than in adults. Those parasites which are

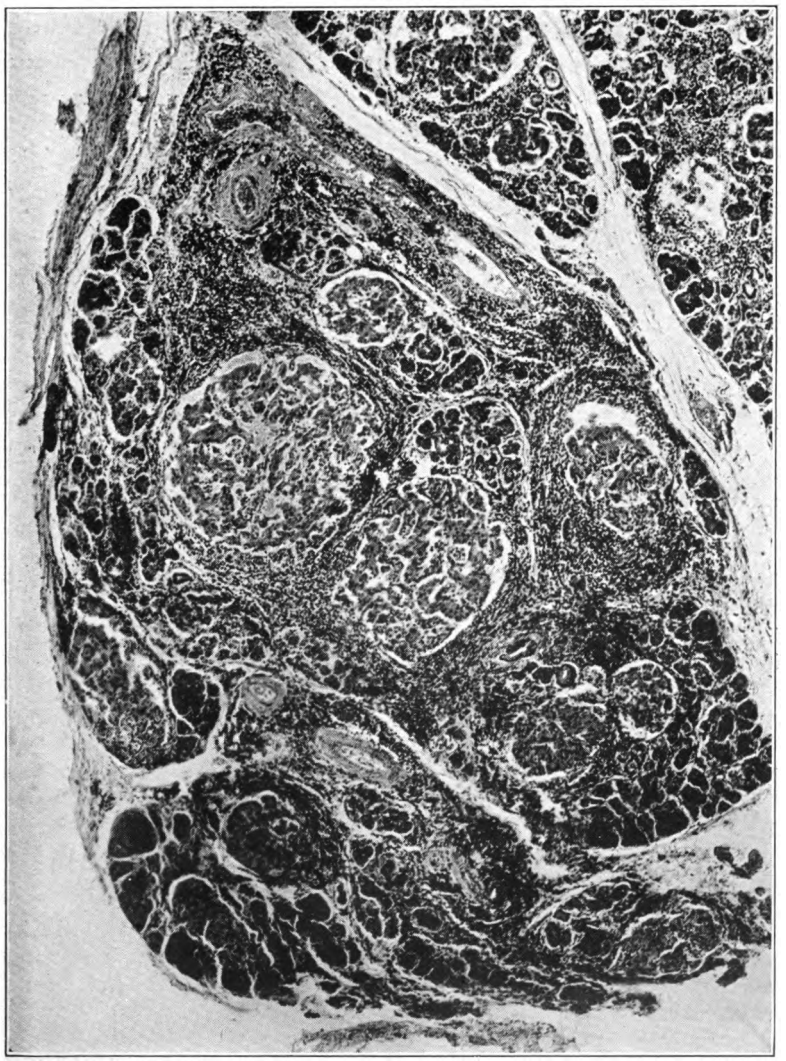

FIG. 1. Low power picture showing islands of large size and eosinophilic infiltration of the surrounding tissues.

capable of passing into encysted form gradually show a diminishing influence on the eosinophiles. If, however, the contents of the cyst gain access to the blood stream either by rupture, or by aspiration and injection, an immediate eosinophilic response results. Of the intestinal parasites, the *Ankylostoma duodenale* stands at the head in its ability to produce an eosinophilic response, values as high as 80 per cent. having been recorded. When it is considered that at the same time there is a marked rise in the total number of leucocytes, it can readily be seen that enormous numbers of new cells have been added to the circulating blood. Malaria in its chronic forms has been known to produce 20 per cent. of eosinophiles.

Certain of the infectious diseases present instances of moderate increases in the number of eosinophiles,—rheumatic fever, scarlet fever, vaccinia, the post-critical period in pneumonia when the eosinophiles which have heretofore been completely absent from the blood reappear. In gonorrhea, especially with the incidence of complications, a moderate increase in the number of eosinophiles has been observed, while extreme values of 25 per cent. have been recorded. Amœbic dysentery has also shown high figures, 47 per cent. having been reported in one case.

In tuberculosis we find the eosinophiles playing a rôle of some prognostic importance for they disappear from the blood in cases of advancing involvement by the tubercle bacillus and reappear only when the reparative processes of the body have succeeded in outstripping the ravages of the disease.

The list of dermatoses with which eosinophilia has been associated is a long and formidable one. It is an almost constant accompaniment of urticaria, eczema, prurigo, iodide and mercury erythemata, and all vesicular and bullous diseases. Psoriasis shows an eosinophilia only inconstantly, but it is invariably present in the dermatitis exfoliativa which often follows psoriasis.

A general eosinophilia is also seen accompanying many of the granulomata and neoplasms. Prominent among these is Hodgkin's disease where figures up to 28 per cent. may be encountered. Curiously enough, higher values may be met with after *x*-ray treatment, percentages up to 68 per cent. having been reported. General sarcomatosis and carcinosis may produce a generalized eosinophilic response even to 45 per cent. in cases of the latter. Lymphosarcoma may also produce a general blood-reaction, but to a less degree.

Local Eosinophilia: The eosinophiles are found widely scattered throughout the body under physiological conditions, both in the fluids of the body and also in the tissues. In the hæmolymph glands they are more numerous than in the ordinary lymph glands. They are said to be absent from the mucous membrane of the œsophagus and stomach but are present in considerable numbers in that of the intestine. A diet mainly of meat or one containing many irritating components is said to increase the number of the eosinophiles in the mucosa. During the digestive periods the number in the spleen increases, while in fasting periods only a few can be found. When present they are found only in the pulp. There are no recorded investigations as to their presence in the salivary glands or the pancreas.

They exist in only moderate numbers in the walls of the respiratory

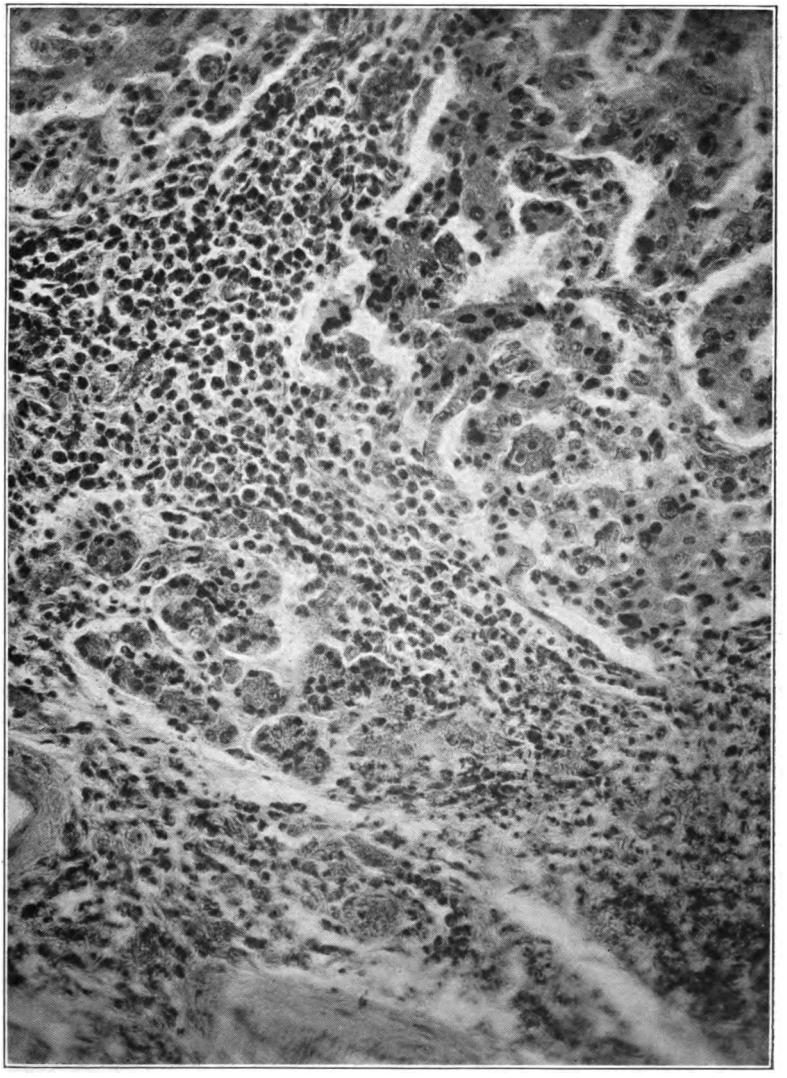

FIG. 2. High power of same showing disordered structure of the islands and the infiltration of the surrounding tissues by eosinophiles.

tract, but are said to present accumulations about the mucous glands of the bronchi.

They may be found in varying numbers in the thymus increasing up to the seventh month and then receding.

In lesions of the gastro-intestinal tract they may be materially increased in number, being found in catarrhal gastritis, atrophic gastritis and especially in tissues showing neoplastic changes. They are supposed to bear a direct relation to the increased mucous secretion of the disordered mucosa rather than to the processes of disintegration. In some forms of appendiceal inflammation they are quite numerous. These accumulations in the mucosa of the intestinal tract are attributed to local immunity reactions comparable to the generalized eosinophilia associated with anaphylactic phenomena.

They are present in the myocardium of cases dying during the course of diphtheria. They are not found in cases proving fatal prior to the seventh day of the disease. Attempts to explain them on the basis of anaphylaxis resulting from the injection of antidiphtheric sera have not been successful, for they have been found as frequently in those who have been and those who have not been treated with serum. They are not present in increasing numbers in comparison with the number of serum injections, and they bear no relationship to the clinical severity of the case. They are found closely gathered about the smaller blood vessels but not in the region of blood extravasations nor near the foci of degeneration.

They are inconstantly present in the pus arising from non-specific inflammations, but in the pus from gonorrheal processes in any site they are abundantly present, increasing in direct relation to the duration of the process until they may make up almost the entire bulk of the suppurative material. In the nasal and bronchial secretions from asthma and hay-fever they are very numerous and may in these instances be largely mononuclear in character. In asthma it has been noted that large numbers of the leucocytes found in the urine may be eosinophiles. The fæces in cases of intestinal helminthiasis may contain large numbers of eosinophilic leucocytes. Pleural exudates often show increasing numbers of eosinophiles as the inflammatory process recedes.

The parasitic lesions of the skin show a local eosinophilia, the cells being arranged either in groups or scattered diffusely through the tissues. Often they are gathered about the smaller blood vessels. In cases of infection with *Trichinella* the eosinophiles are not strictly limited to the immediate vicinity of the parasite, but they may be found throughout the interstitial inflammatory tissue. In lymph node involvement by *Filaria* the eosinophiles may be found in large numbers occupying both the lymph sinuses and the lymph cords. The lymphatics may also be found to contain great numbers of eosinophiles. *Balantidium coli* is also capable of producing a marked eosinophilia, the infected areas of the colon containing many of these cells.

The dermatoses in a similar manner show a local eosinophilia, the tissues surrounding and underlying the lesions often being tightly packed with eosinophiles. The skin diseases capable of producing a local eosinophilia are identical with those which are responsible for the similar generalized blood reaction.

The local eosinophilia about neoplasms is often of considerable importance. This question presents many obscure and puzzling features for no one constant factor can be found exercising any marked influence upon this specialized tissue reaction. One form of tumor may in one site be accompanied by a marked eosinophilia only to find a similar reaction completely lacking in a similar tumor in another region, and one form of tumor in a given region may supply many eosinophiles, whereas a different tumor in the same tissue will show none. In general, however, it may be stated that those tissues which are exposed to the greatest irritation are those in which the eosinophiles are the most numerous.

The carcinomata are fairly regularly accompanied by a moderate eosinophilic infiltration, the uterus being the tissue which is capable of furnishing the greatest numbers of these cells. They are also present to a lesser degree in sarcomata of all types. They are usually infrequent in the hypernephromata. Benign growths may also show an eosinophilia, but less regularly and to a slighter degree, than the malignant growths.

The lesions of periarteritis nodosa show regularly a diffuse admixture of eosinophilic cells.

CASE REPORT

The child whose pancreas is the subject of this paper was born on the 25th of March of this year at the Nursery and Child's Hospital. It was the last of fourteen pregnancies, one of which terminated in a still-birth; all the others however, including this one were normal in all respects. The child was living until labor began, but as it was a very large child, weighing over ten pounds and being a breech presentation with a long difficult labor, extraction was protracted and the child was born dead. There were no external abnormalities, no stigmata of syphilis, and all the organs were found in an approximately normal condition. The pancreas was grossly quite normal. The cause of death was ascertained to be a fracture between the third and fourth cervical vertebrae, consequent upon forcible extraction in the breech position. No suspicion of anything pathological was aroused in the routine microscopical examination except for a slight degree of degeneration in the parenchymal cells of the liver, kidneys and adrenals, until the pancreas was reached, where a most unusual and interesting condition was found. This change affected all the constituents of the pancreas, the islands of Langerhans, the interstitial tissue and last and least the acinar tissue. The same condition existed in all parts of the organ examined.

The islands were enormously increased in size and almost visible to the naked eye. They were much distorted and their usual orderly internal structure was much obscured. They were made up chiefly of two types of cells: (1) A cell which comprised the main bulk of the island and was large with a granular deep staining cytoplasm and an ill-defined cell outline. The nuclei differed much in size, some were very large indeed and presented a clear protoplasm, a definite chromatin network, and in some cases a distinct nucleolus. The cytoplasm of the cells in many areas resembled a syncytium. These cells suggested in many of their properties neoplastic cells. (2) The second type of cell was much less numerous and was arranged principally about the periphery of the islands. It had a small darkly staining nucleus, more or less oval in outline, in which no chromatin network could be made out. Its cell outline was somewhat more definite than that of the preceding cell, and its cytoplasm took a pinker stain. Occasional eosinophiles could be seen in among the cells of the island. In the spaces which surrounded the capillary loops could be seen numbers of beautifully granulated eosinophiles, which were in greater part multilobular, although mononuclear cells were present in fair numbers. In the connective tissue of the capillary loops the eosinophiles seemed to be surrounded by delicate connective tissue strands. The connective tissue of the pancreas presented the most extraordinary eosinophilic infiltration, the entire tissue having been simply converted into eosinophilic tissue, each cell, in many instances, surrounded by delicate connective tissue fibrils. Between the eosinophile cells could be seen occasional connective tissue cells and only very infrequently a polynuclear leucocyte. The tissue was so densely infiltrated with eosinophiles that it was difficult to demonstrate any particular condensation about the blood vessels. The capillaries were engorged and the lining endothelium seemed enlarged and swollen, but only occasional eosinophiles could be found within the capillaries. There was a large amount of free eosin-staining granular material present in the section. Scattered here and there singly and in small clumps between the cells could be seen long needle-like crystals pointed at each end and somewhat thicker at the

middle, which took a pink stain, and seemed to be typical Charcot-Leyden crystals. The acinar tissue was much reduced in amount and the acini were in large part isolated from one another by a uniform increase in the amount of inter-acinar connective tissue which appeared oedematous and was loaded with eosinophiles. The majority of the acinar cells appeared quite normal but occasional vacuolated cells and indeed entire degenerating acini could be found. The eosinophile cells did not invade the acini.

Attempts to clear up the etiology of this condition have been without success. Tissue stained by the Levaditi method and examined for spirochaetae has not disclosed any of these organisms. Efforts to find bacteria in preparations stained by the Gram method and with Giemsa's stain have also been unsuccessful.

The question of the origin of the eosinophiles, whether by emigration from the blood vessels or by local production will be left open.

It is equally impossible to give any definite opinion as to the underlying cause for this peculiar picture, but it would seem that it was associated with the islands of Langerhans. The appearance of the cells of the islands indicated that some unusual process was in course there and it is conceivable that some abnormality in their metabolism may be responsible for the eosinophilic infiltration.

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Discussion:

DR. PAPPENHEIMER: I would like to ask the Society for suggestions about this case. It seems to be an unusual condition and none of the long list of possible causes of eosinophilia, which Dr. Riley has cited seems applicable here. In no inflammatory condition with which I am familiar, is the exudate composed entirely of eosinophilic cells. There are, of course, a great many eosinophiles in gonococcus infections of the mucous membranes, but in Dr. Riley's case the exudate is exclusively eosinophilic. Active blood formation in and about the pancreas is not uncommon in new-born infants. In this case, however, the absence of other blood elements and of active hemato-

poiesis in the liver—and the fact that the eosinophiles are almost all polymorphonuclear makes it certain that the areas are not to be regarded as blood-forming islands.

DR. EISENBREY: The only thing I have seen resembling this was in a case of Hodgkin's disease, where the eosinophilic infiltration was very nearly as marked. Occasionally in epithelioma of the cervix you see the exudate composed almost entirely of eosinophiles, but these conditions have no bearing on this particular case.

PATHOLOGICAL FINDINGS IN A CASE OF AMAUROTIC FAMILY IDIOCY

SARA WELT-KAKELS, M.D.

As it is the writer's intention to publish later a paper upon this subject *in extenso,* only a brief abstract of the report will be given on this occasion in connection with the demonstration of sections from a case of amaurotic family idiocy.

A general review of the contributions to the present knowledge of the subject will be omitted at this time and attention will be given to the discussion of the case. Pathological findings were demonstrated by microscopical sections of the brain, spinal cord, and spinal ganglia of a girl who died from this disease when 23 months old. The nervous tissues showed widespread degenerative processes involving the gray nerve cells, consisting of balloon-like swellings of the cell body and dendrites with the disappearance of the Nissl bodies and a peripheral displacement of the nucleus. In more advanced degeneration, the cells appeared like structureless masses. These alterations of the cells were especially well demonstrated in sections stained with Bielschowsky's stain.

Sections of the ductless glands of the patient were also exhibited. The thymus showed marked increase in connective tissue, mainly in the septa. Hassal's bodies appeared to be increased in amount, with disappearance of thymic parenchyma.

The thyroid sections showed no changes.

The adrenals showed slight parenchymatous degeneration; the cortical substance was somewhat shrunken.

The hypophysis showed increase in the number of acidophilic cells.

The examination of the ductless glands seemed to be very opportune, since Dr. Harlow Brooks reported marked alterations in the thymus, adrenals and pituitary glands in a case of amaurotic family idiocy, juvenile type. These lesions suggested to Dr. Brooks atypical functional activity and a possible causal relationship in this disease. The findings in the ductless glands of my case did not seem to justify the assumption that they were either direct or indirect factors in the causations of this fatal malady, nor were the lesions found in the endocrinous glands pathognomic for amaurotic family idiocy, infantile type.

A careful comparative study of ductless glands from children of approximately the same age, which, by courtesy of Dr. A. M Pappenheimer I was given the opportunity to examine at the Nursery and Child's Hospital, seemed to show that similar changes in the endocrinous glands occurred in children who succumbed to other diseases.

Discussion:

DR. PAPPENHEIMER: Was the sympathetic system investigated?

DR. WELT-KAKELS: No, so far as I know, in none of the cases.

DR. LEVIN: Did I understand that some chemical examination had been made of the central nervous system, or not? Was any thing found chemically that would indicate where the trouble lay? Most probably this is a metabolic condition, and not an infection. In this case some abnormal products in the brain may indicate the condition.

DR. WELT-KAKELS: Mott found diminution of sulphur and phosphorus. This was not corroborated by Heiman, Cohn and Bookman.

MORPHOLOGICAL CHANGES INDUCED IN TUMORS UNDER THE INFLUENCE OF ROENTGEN RAYS AND RADIUM

ISAAC LEVIN, M.D.

(*From the Department of Cancer Research of the Montefiore Home*)

The physical properties of Roentgen and gamma rays emitted by radio-active substances are completely analogous to the rays

of light. Both kinds of rays represent, in accordance with the recent physical conceptions, waves of ether. The wave length of actinic rays, i. e., of Roentgen and gamma rays, are a thousand and more times shorter than the shortest ultra-violet rays of light. As a result the rays of light are absorbed completely by the first superficial layers of a substance which they traverse. The actinic rays, on the other hand, penetrate into deeper layers of the substance, and only a fraction of them is lost through absorption by the more superficial layers.

The biological action of the two kinds of rays is also analogous. This analogy is very evident in the so-called *x*-ray burn of the skin. When a large dose of soft *x*-rays is applied to the unprotected skin there takes place an erythema, blistering and ultimately the condition is qualitatively identical with a sunburn and only differs from it in degree. The browning of the skin which takes place as a result of an *x*-ray burn, or occasionally after *x*-raying of the skin even without the formation of a burn is identical with the pigmentation of the skin after a sunburn. Here again the difference is only in degree.

Fr. Bernig in a recent review states that the rays of light, or rather of the ultra-violet light, which is the only biologically active part of the spectrum, produce the following effect on the skin: Direct destruction of the cells; thrombosis of the blood vessels (through the direct influence of the rays on the endothelium and musculature of the vessels) and sero-haemorrhagic inflammation. The latter ends with the formation of hypertrophic connective tissue. It will be seen later that these morphological changes are very similar to the changes induced in tissues by actinic rays.

The analysis of a biological action of any agent is much simpler in the uncomplicated cellular structure of a plant or lower animal than in a vertebrate. A. Richards came to the following conclusions from his studies on the effect of *x*-rays on the rate of cell division in the early cleavage of *Planorbis*. The first effect of exposure to *x*-rays upon the rate of cleavage of the eggs of *Planorbis* is to stimulate mitotic activity. Following the phase of acceleration a phase of depression sets in; the end result is a marked retardation in the development of the egg.

In a vertebrate the actinic rays produce a biological effect on all the tissues of the organism, but the degree of injury varies greatly with the different tissues. It may be stated as a general rule that tissues consisting of less differentiated, younger cells also cells in a state of active proliferation are most deeply influenced by the rays. It is probable that in these complex vertebrate tissues the first effect of the rays also consists in an acceleration of the cellular functions. But it is very difficult to demonstrate such a phenomenon morphologically. Histologically one sees finally complete necrosis of the cell. Every tumor consists of undifferentiated young cells in a state of active proliferation, consequently a strong selective biological influence of the rays on tumors must be considered certain *a priori*. The morphological changes which take place in tumors under the influence of the rays differ with the different types of tumor and it may be well to consider them separately.

Carcinoma.—The first morphological changes which occur in carcinomatous tissue under the influence of actinic rays are observed in the tumor cells themselves and are manifested by the vacuolization of the protoplasm, pycnosis of the nuclei, karyolysis and complete necrosis of the cell. All this is accompanied by a round cell infiltration which replaces the destroyed carcinomatous cells. Somewhat later there begins formation of dense sclerotic connective tissue poor in blood vessels. This connective tissue formation may become very extensive, surround islands of carcinomatous cells and assist in the destruction of the latter. The following case of carcinoma of the sigmoid with metastatic dissemination in the peritoneum which came to autopsy after six months of continuous *x*-ray treatment demonstrates the importance and extent of this connective tissue formation.

The patient died of acute intestinal obstruction. At the autopsy there were found in the peritoneal cavity several loops of the intestines adherent by old adhesions to the posterior surface of tumor mass in the sigmoid. The peritoneum, especially in the pelvis, was studded with numerous white plaques, varying in size from one mm. to one-half cm. in diameter—the larger ones were

quite firm to the touch. On section the mesenteric lymph nodes were rather small and reddish in color.

Microscopical examination of a section taken through two loops of the small intestine which were firmly bound together by old adhesions, showed that the adhesions consisted of a thick layer of connective tissue containing occasional nests of tumor cells. These nests were rather more abundant, however, in the muscular layers of the intestine than in the fibrous tissue connecting the loops. The tumor cells stained very deeply.

Another section taken from the edge of the colostomy wound showed a bit of skin with a wide zone of connective tissue beneath in which there were occasional groups of tumor cells in the muscular layers and mucous membrane of the intestine. There were relatively few groups of tumor cells in the muscular layers, but the mucous membrane was rather densely infiltrated with tumor. In the muscle, especially, one could see groups of tumor cells, apparently degenerated, in the midst of a mucoid material of the character that is found in the so-called colloid carcinomata.

The peritoneal nodules were composed of dense connective tissue, with occasional groups of tumor cells, which, as elsewhere, stained poorly. No follicles of colloid material were present. In some nodules no tumor cells were found.

Sarcoma.—The morphological changes induced in sarcomatous tissue by actinic rays is identical with those induced in carcinoma. The following case of a giant cell sarcoma of the lower jaw illustrates this effect. A small piece was removed for microscopic examination which showed a sarcoma with numerous giant cells and actively growing spindle cells. Following eight weeks of combined radium and *x*-ray treatment another section was taken from the same region from which the previous one was obtained. The section showed a very loose connective tissue, relatively poor in cells and beneath this a denser zone of cellular connective tissue. No giant cells or distinct spindle cells were present. A radiogram taken at the same time showed that the whole tumor was surrounded by a great deal of newly formed bone. Examination through the mouth showed the tumor to

have completely disappeared and there was present instead a large cavity lined by a shell of bone.

Rhinoscleroma.—Infectious granulomata, whether tuberculous, syphilitic or of any other kind, are influenced by the actinic rays as lympho-sarcomata. The lymphoid cells are destroyed and replaced by dense sclerotic fibrous connective tissue. Rhinoscleroma is an infectious granuloma, characterized by the presence in the granulation tissue of the so-called Mikulicz cells. The latter are degenerated lymphoid cells, enlarged in size, inside of which may be found frequently the Frisch bacillus, the etiological factor. Under the influence of radium the observed cases showed a disappearance of the obstructing swelling of the naso-pharynx. The microscopic examination showed that the granulation tissue was completely replaced by dense connective tissue.

CONCLUSION

Thus the most generally observed morphological change in tumor tissue under the influence of radiation is the extensive formation of sclerotic connective tissue. Some observers maintain that this new connective tissue formation is the only direct effect of radiation. The destruction of the tumor cells is secondary and is due to lack of nutrition. This opinion cannot be accepted as true. In the first place, as was shown above, the first change noted in carcinoma was the destruction of the cells and only subsequently did the connective tissue form. Moreover, in certain conditions, for instance rodent ulcer of the skin, the epithelioma heals, is covered with skin epithelium and there is no formation of connective tissue.

Other investigators assert that the destruction of the tumor cells is the only direct affect of radiation. The formation of connective tissue, in accordance with this view is secondary to the accumulation of dead tumor cells and is analogous to formation of connective tissue about foreign bodies. This assumption is also hardly tenable. In the first place the amount of connective tissue formation in the peritoneal nodules of the carcinoma of the sigmoid reported above was entirely out of proportion to the

number of carcinomatous cells present. Moreover, if such young connective tissue were formed only by the stimulus of dead tumor cells, then the actinic rays subsequently would dissolve this connective tissue as easily as it dissolves a keloid. But this does not take place and the amount of connective tissue usually increases with subsequent radiations.

It must be concluded then that morphological changes which take place in tumor tissue under the influence of actinic rays are two-fold. There occurs an inhibition and ultimate destruction of the tumor cells with irritation and consequent proliferation of surrounding connective tissue. But the beginning of this new connective tissue cannot be looked for in the normal tissue surrounding the tumor. The post-mortem study of the carcinoma of the sigmoid showed that there was no new connective tissue formed anywhere in the normal organs under the influence of radiation. The source of this new connective tissue must be looked for either in the stroma of the tumor or in the round cell infiltration which always closely follows the destruction of the tumor cells by the rays.

It may be stated then that the destruction of the tumor cells is the primary and the formation of new sclerotic connective tissue a secondary but at least as important a phase in the morphological changes which take place in tumors under the influence of actinic rays.

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Discussion:

DR. SITTENFIELD: I would like to ask Dr. Levin whether he has studied vascular changes in the tumor and whether he has any notion as to just how the cells are influenced,—whether by dissociation of the chemical component parts of the cells or by destruction of the generative apparatus of the cell as held by Wassermann, or by inactivation of intracellular ferments?

DR. LEVIN: So far as blood vessels are concerned, there takes place a condition similar to endarteritis obliterans which decreases the amount of blood supplied to the tumor causing inhibition and death of the tumor cell. As to Dr. Sittenfield's second question, it is impossible at present to determine the mechanism of the biological action of the actinic rays.

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CONTENTS

AMYLOIDOSIS: (*a*) INCIDENCE. (*b*) REPORT OF CASE WITH EXTENSIVE AMYLOID-LIKE DEPOSITS IN ORGANS NOT SHOWING ANY OF THE CHARACTERISTIC REACTIONS

R. A. LAMBERT, M.D.

(*From the Pathological Laboratory of Montefiore Hospital and the Department of Pathology of the College of Physicians and Surgeons*)

(*a*) INCIDENCE

Among fifty-five autopsies performed at Montefiore Hospital during the past eight months nine cases of amyloidosis have been encountered, an incidence of 18 per cent. Chronic pulmonary tuberculosis was the cause of death in twenty-one cases, eight of which, or 38.1 per cent., showed a deposition of amyloid in various organs.

As will be seen from the accompanying table these figures suggest that amyloidosis is far more common in this hospital than in

other institutions from which statistics on this point are available. Fortunately, we are able to compare these figures with those obtained from the records of the Presbyterian Hospital where during the past seven years only six cases of amyloidosis have been observed in approximately eight hundred and fifty autopsies, an incidence of 0.7 per cent.

Also at the College of Physicians and Surgeons, where autopsy material is received from various hospitals, only twelve cases of amyloidosis have been seen in nearly one thousand autopsies. Statistics from foreign hospitals show, too, a far lower incidence. It has seemed to us that a consideration of the possible causes for this striking difference in frequency should prove of interest.

TABLE

	Chronic Tuberculosis	Cases Showing Amyloidosis	Incidence, Per Cent.	Non-Tuberculous Cases	Cases Showing Amyloidosis	Incidence, Per Cent.	Total Autopsies	Total Number Cases of Amyloidosis	Incidence, Per Cent.
Montefiore Hospital.....	21	8	38.1	34	1	3.0	55	9	16.4
Presbyterian Hospital..	50	2	4.0	800	4	0.5	850	6	0.7
College of Physicians and Surgeons	158	9	5.7	842	3	0.35	1,000	12	1.2
Vienna (Blum's statistics)	2,500	221	8.8	15,653	76	0.49	18,153	297	1.5
Kiel (Wicht's statistics).							2700	97	3.6

It should be stated in the beginning that the number of autopsies in the Montefiore series (fifty-five) is rather small for any conclusive statistical study, but the fact that only sixteen[1] cases of amyloidosis have been found in one thousand, eight hundred and fifty autopsies outside of Montefiore Hospital goes far to prove that the high incidence there cannot be regarded as accidental.

In discussing this problem with Dr. Wachsmann, Superintendent of Montefiore Hospital, and others, it has been suggested that the patients in that institution differ from those in other general hospitals in at least three respects: (1) Most of the patients are foreign born. This was true of all of the cases of amyloidosis;

[1] Eighteen cases are recorded in the table but two of these were Montefiore cases, the material from which was sent to the College of Physicians and Surgeons.

(2) All patients belong to the Jewish race; (3) The tuberculous patients admitted differ in certain respects from those in many other hospitals.

Regarding the first factor, namely, the nationality of the patient, it has been stated by many who have attended autopsies in Berlin and Vienna, that amyloidosis is much more common in Europe than in America. The statistics from Vienna and Kiel (see table) seem to disprove this idea, since the percentage of amyloidosis in total number of autopsies as well as in cases where death was due to tuberculosis is not much higher than at the College of Physicians and Surgeons, and not nearly so high as in the Montefiore series.

At Vienna in calculating the percentage of tuberculous cases showing amyloid deposits, cases of acute general miliary tuberculosis and tuberculous pneumonia were probably included, whereas such cases were carefully omitted in the preparation of our statistics. We made this selection of tuberculous cases, firstly, because amyloid is practically never found in acute tuberculosis; and, secondly, because all the cases at Montefiore Hospital were chronic. Therefore a fair comparison necessitated a selection of cases of the same type at the other institutions. If we should include in our statistics from the College of Physicians and Surgeons and the Presbyterian Hospital deaths from acute tuberculosis the percentages of amyloidosis in tuberculosis would fall considerably lower than those for Vienna and Kiel.

Looking into the question of nationality of the six cases of amyloidosis at the Presbyterian Hospital, we find one Italian, one Englishman, two Hungarians, one American of German parentage, and one American negro. The percentage of foreign-born patients admitted to the hospital is about 40 per cent., but if to this group are added those of foreign parentage the percentage of "foreign" patients would probably reach 75. It is seen therefore that these figures do not give much support to the idea that foreigners are very much more susceptible to amyloid disease.

The second suggestion, that of a racial predisposition, is one upon which our available statistics are not altogether conclusive. At the College of Physicians and Surgeons no record of race has been kept. At the Presbyterian Hospital, although about 12 per cent. of the admissions are Hebrews, autopsies upon people of

Jewish faith are rare, comprising less than 5 per cent. of the total number. Thus we are able to compare the records of a hospital where all are Hebrews with those of another where there is only a small percentage of such cases. This comparison (see table), which shows at Montefiore Hospital an incidence of amyloidosis nine times as great in cases of chronic tuberculosis and six times as great in non-tuberculous cases as at the Presbyterian Hospital, certainly suggests a definite racial susceptibility. However we hesitate to form any conclusion on this point because a careful study of the cases at the two institutions, which brings us to the third possible predisposing factor, shows that the types of patients, especially those of chronic tuberculosis, admitted to the two institutions differ very materially.

The patients coming to autopsy from the tuberculosis division of Montefiore Hospital show as a rule far advanced pulmonary tuberculosis of long duration (average of those coming to autopsy, three years and four months). At the Presbyterian Hospital the cases of chronic pulmonary tuberculosis give a history usually of short duration (average of those coming to autopsy, nine months). While we have included in the fifty Presbyterian Hospital cases only those which were obviously chronic with cavity formation in lungs, or extensive bone lesions, we do not think that the comparison between these and the Montefiore cases is altogether satisfactory.

In order to settle conclusively the question of a racial susceptibility it will be necessary to obtain statistics from an institution receiving non-Jewish patients, more nearly of the type found at Montefiore Hospital.

The experimental work of Davidsohn and others, who have shown that certain strains of mice and rabbits are much more susceptible than others to the development of amyloidosis, is at least suggestive in this connection.

The tentative conclusions from this brief review of twenty-seven cases of amyloidosis seen in New York among nineteen hundred and five autopsies are as follows:

1. The influence of nationality upon the incidence of amy-

loidosis is negligible. That the condition is less common in America than in Europe is doubtful.

2. A predisposition to amyloid disease on the part of Hebrews is suggested, though not proved, by the high incidence observed at Montefiore Hospital.

3. The most important factor in determining the incidence of amyloidosis in any hospital is the type of patient admitted. Tuberculosis of long standing, involving extensive tissue destruction, is the condition most often associated with amyloidosis (70 per cent. in our cases).

(*b*) REPORT OF CASE WITH AMYLOID-LIKE DEPOSITS IN ORGANS

In eight of the nine cases of amyloidosis observed at Montefiore Hospital, and in all of the eighteen cases at the Presbyterian Hospital and the College of Physicians and Surgeons, the amyloid-containing organs showed the usual reaction with iodine. In one of the Montefiore cases, however, the reaction was entirely negative.

The case was that of a young man, twenty years old, who had shown symptoms of pulmonary tuberculosis for two years: cough, expectoration, hemoptysis, afternoon fever, etc.

At *autopsy* lungs showed extensive tuberculous lesions with numerous cavities in right lung. Spleen weighed 800 grams, was hard and on section presented the picture of a typical "sago" organ. The liver weighed 2,200 grams, was very firm and friable and showed the characteristic bacon-like translucency. In the kidneys no striking gross changes were apparent. The adrenals were rigid as though preserved in formalin.

Microscopical Examination: In the spleen, liver, adrenals and glomeruli of kidneys an extensive deposition of a hyaline pink-staining material was found, which presented the distribution characteristic of amyloid.

Application of iodine to the gross specimen, as stated above, gave no reaction. Negative results were likewise obtained with methyl-green and iodine-green. Methyl-violet gave in places a very faint reddish tinge which appeared to be more pronounced in the hyaline material in immediate proximity to the blood vessels. This faint staining was clearly seen in the liver sections. The

tests were applied on fresh tissue and on specimens fixed for a short time in formalin. Some of the sections were first treated with weak acetic acid in order to neutralize any alkali present.

There seems little doubt, therefore, that we are concerned here either with deposits of an incomplete amyloid material or a general hyalinosis, a condition not recognized by those who have worked in this field. It has been clearly demonstrated by Davidsohn and others in the experimental amyloidosis of mice and rabbits that there are at least two stages in the development of amyloid. In the earlier stage the deposits do not give the usual reaction. The reaction with the methyl-violet group of dyes appears first, usually in the spleen. The iodine reaction is obtained later. Only the completely finished product, which is found rarely in organs other than the spleen and liver, gives the iodine-sulphuric acid reaction. In the present case such an extensive deposition would suggest a late rather than an early stage. It is possible, however, that there may have been a very rapid formation and deposition of the incomplete amyloid during the last few weeks of the patient's life, and that sufficient time had not elapsed for its complete development. So far as we have been able to find out no case like this one, with such extensive deposits giving none of the usual reactions, has been described.

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Discussion:

DR. FIELD: One reason that would suggest itself to me why we see so few cases of amyloidosis is that most of our material is obtained from hospitals which have an "acute" service. I imagine that more is seen on the Island in the almshouse and among their chronic cases than in Bellevue where the service is "acute." This has impressed itself on me since going down to the Neponsit Hospital, where children with bone and joint tuberculosis are treated. The number of cases in which the clinicians have diagnosed amyloidosis is comparatively large. In Louisville I saw, in my two years there, more amyloidosis than I have seen in my twelve years in New York. The cases were found among negroes who had had chronic suppu-

rative lesions extending over periods of many years. I do not think that the suppuration is limited to any one type of organism. The only constant feature in my experience has been a suppurative process, though, of course, this generally showed many types of microorganisms.

DR. ZINSSER: I would like to ask whether amyloid change has any relation to any particular type of suppuration. Is it associated with any specific variety of microorganisms or is it the result of suppuration in general?

DR. LARKIN: We must ask what is amyloid degeneration. Chemists have not given us definite information as regards its chemical content. We are not in a position to tell the different stages of amyloid or hyaline degeneration. Neither macroscopical nor microchemical tests are absolutely proved. I would be chary of putting down such a specimen as amyloid, where the microchemical test does not confirm it. I think Dr. Zinsser's question is a pertinent one as to what are the factors that produce it. We look for amyloid degeneration in chronic suppurative conditions, bone tuberculosis, psoas abscess, and so on. There are a number of suppurative conditions of which we do not know the character, which do not produce amyloid. We must differentiate these cases from those giving the microchemical test. This specimen does not represent amyloid conditions *per se*. It is one of the intermediate groups.

DR. LAMBERT: Replying first to Dr. Zinsser's question: in the experimental production of amyloid it has been shown that almost any pyogenic organism may be used. Killed cultures are quite efficacious.

Regarding Dr. Field's last statement, I think that the common association of amyloid disease with tuberculosis is too well established to warrant discussion. In Blum's series at Vienna (two hundred and ninety-seven cases in eighteen thousand one hundred and fifty-three autopsies) tuberculosis was the etiologic factor in 79 per cent.: in our series, 70 per cent.

With Dr. Field's other remarks I am in thorough accord. His experience makes me feel certain that the high incidence at Montefiore Hospital is probably to be attributed to the very chronic type of tuberculosis treated there.

REPORT ON TWO FORMS OF CARDIAC ABNORMALITY

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The study of the two hearts which form the basis of this report is presented more with the idea of placing the results on record than of giving in connection with it any extended discussion of the anatomical or pathological features of the organs. The

material was obtained from the Pathological Laboratory of the New York Nursery and Child's Hospital. During the past year we have met with almost all the common types of cardiac abnormality and in addition we have found three conditions of more than usual interest:

(*a*) Complete transposition of the arterial trunks.

(*b*) Complete absence of the interventricular septum.

(*c*) Aortic atresia and rudimentary left ventricle.

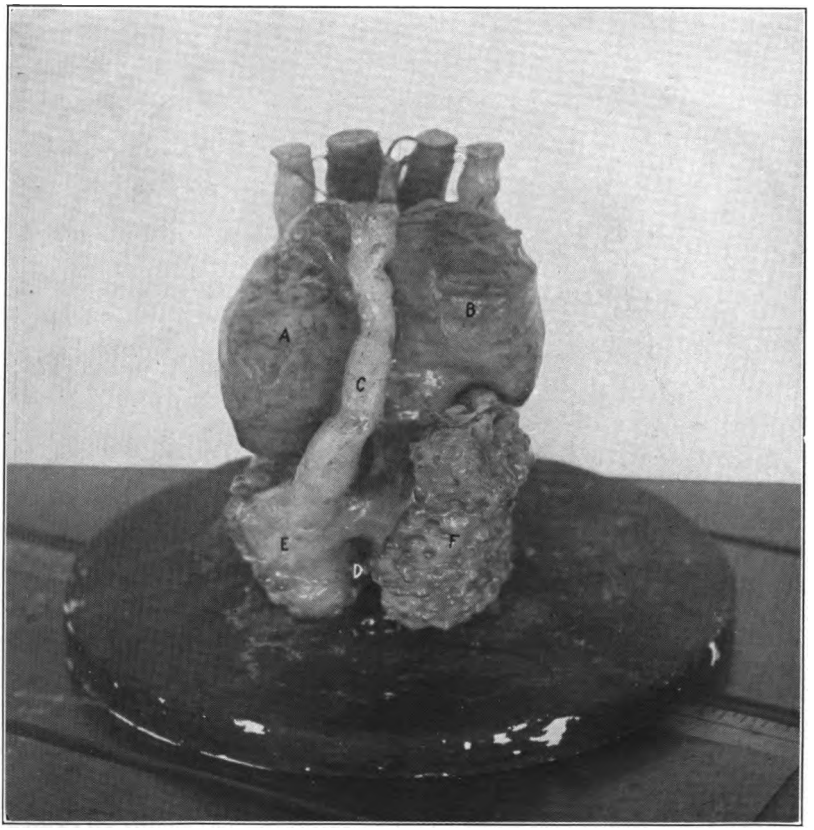
The first two will be shown at this meeting; the third will be made the subject of a separate report at some later date.

COMPLETE TRANSPOSITION OF THE ARTERIAL TRUNKS

CASE I. *Pathology.*—In this case, we find the ventricular portion of the heart to be normal in all its features; position, size, and composition of its costo-chondral surface. The heart is normally divided by its interventricular groove. The right ventricle externally appears somewhat larger than the left and forms the apex of the heart, but upon opening the organ, we find that the cavity of the left ventricle is larger than that of the right. The walls of the right ventricle are thicker than those of the left. The auriculo-ventricular valves are thin, delicate, and present extra flaps; the right auriculo-ventricular orifice being guarded by a valve which presents four flaps, the left auriculo-ventricular orifice by a valve with three flaps. The auricles are normally formed and separated from one another and there are no defects in the interauricular septum. The foramen ovale is still patent along its anterior border.

The great vessels present a condition of complete transposition, the aorta arising from the right ventricle, the pulmonary artery from the left. They emerge from the heart in an almost directly transverse plane close together and near the anterior aspect of the heart. They both pass upward and somewhat backward. The aorta then sweeps to the left and posteriorly over the bifurcation of the pulmonary artery, giving off its three great vessels from its superior aspect. The inferior aspect of the vessel receives the ductus arteriosus which is comparatively long, twisted,

and patent. The aorta then passes over the root of the left lung. The pulmonary artery passes upward and backward under cover of the aorta and divides into three vessels, the ductus arteriosus.



Photographs of reconstructions of the cardiac apparatus in three cat embryos—7, 9, 11 mm.—in length, showing the effect of torsion on the truncus arteriosus and the division of that vessel into the aorta and the pulmonary artery.

FIG. 1. 7 mm. cat embryo. *a*, right auricle; *b*, left auricle; *c*, common arterial trunk; *d*, interventricular septum; *e*, right ventricle; *f*, left ventricle.

which arises slightly to the left of the bifurcation, and the two pulmonary arteries. The coronary arteries are derived from the

aorta. The semilunar valves are normal both in number and arrangement as are also the pulmonary veins.

In this case we have an arrest of torsion of the great vessels whereby the orifice of the aorta remains on the right side, that of the pulmonary artery on the left. The interventricular septum,

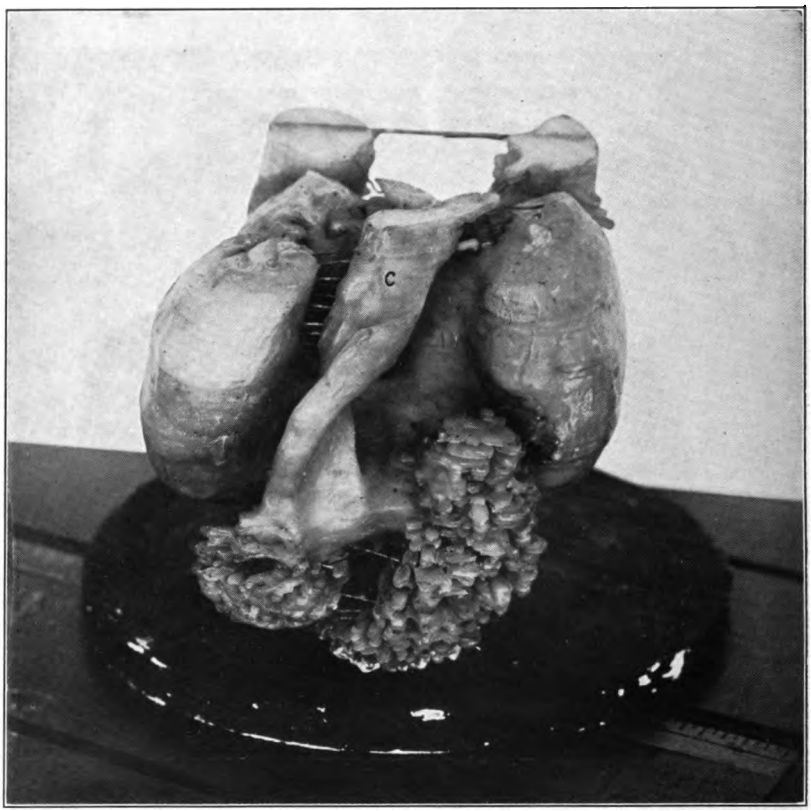


FIG. 2. 9 mm. cat embryo. *c*, common arterial trunk. The truncus shows here the effect of the torsion.

rising from below and coming in contact with the septum trunci, establishes connection between the aorta and the right ventricle, and the pulmonary artery and the left ventricle. The difficult thing to reconcile with this course of events is that in this case

the ventricles have obeyed the tendency to rotate and have taken up their normal position, whereas the truncus which is supposed to obey the same factors in its rotation has completely ignored these factors and has remained unrotated.

Transposition of the Arterial Trunks.—According to the teachings of Rokitansky, transposition of the great vessels, *Rechtslage* of the aorta, as well as certain types of developmental stenosis of the aorta and pulmonary artery, are due to irregularities in the formation of the septum within the aortic bulb and to its malunion with the interventricular septum.

Types.—(*a*) Complete transposition in which the vessels arise from the ventricle to which they do not normally belong.

(*b*) Corrected transposition in which the vessels arise from the proper ventricle but present an inverted relationship to each other.

(*c*) Partial transposition.

In studying these conditions it is necessary for us to keep in mind the processes through which the heart passes in its development in order that we may understand the anomalies which arise through arrest of development or perverted development. In order that these factors may be clear in our minds, it may be well for us to review the steps in the development of these structures.

As will be remembered, the primitive heart tube in its growth becomes twisted upon itself in the shape of the letter S, the venous end being situated posteriorly and to the left in the position where the auricles will develop; in front of the venous end of the heart tube lies the ventricular portion and passing upward mesially and cephalad from the ventricular portion lies the common arterial trunk. There are two fixed points to be considered in order that we may understand the process of torsion which is to determine the picture in the truncus; the first, where the venous end of the heart enters the pericardial sac; the second, where the arterial trunks leave the pericardial sac. Continued growth within the pericardial sac along the direction already initiated by the S-shaped tube produces a torsion of 180 degrees of the common truncus by which the relationship of the adult aorta and the pulmonary artery is produced; this torsion is from the left to the right. By the time that this torsion has begun to make itself felt, the process of separation between the aorta and pulmonary artery has been initiated. This separation is produced by the appearance within the cavity of the truncus of two sets of ridges which according to their relationship with the ventricle, are called proximal and distal. The proximal set of two may be called ridges *A* and *B*, and a distal set of four, ridges 1, 2, 3 and 4. The result of the external forces of rotation or torsion on these ridges is the assumption by them of a spiral twist as they pass toward the heart along the interior of the tube. This spiral twist takes a clockwise direction from above downward and to the right; on the exterior of the tube can be found furrows which correspond to the internal ridges.

We will now follow in some detail the origin of the two sets of ridges

and their behavior in dividing the tube into the two large vessels. The ridges arise on sides of the tube opposite one another; the ridges *A* and *B* in the lower half, the ridges 1, 2, 3 and 4 in the upper half, of the truncus. They are so arranged that as they spiral downward in a clockwise direction one ridge of the proximal set meets and fuses with one ridge of the distal set

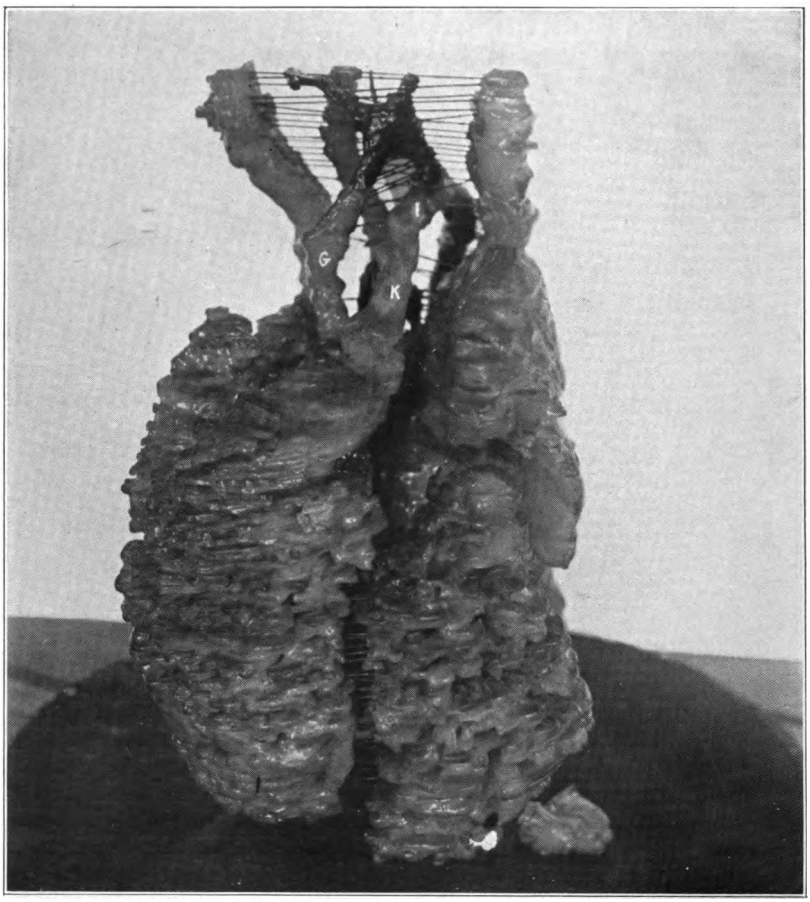


FIG. 3. 11 mm. cat embryo. *g*, aorta; *k*, pulmonary artery; *i*, ductus arteriosus. Complete separation of the truncus into the aorta and the pulmonary artery.

on either side of the tube. We have thus in the composition of each ridge three parts; one horn of the septum aorto-pulmonalis (will be described in detail later); one of the ridges 1 and 3 and one of the ridges *A* and *B*. Ridges 1 and 3 are large, 2 and 4 are small.

Prior to this there has been a separation of the fourth and sixth aortic arches external to the pericardial sac into what will later become the adult aorta and pulmonary artery. This so-called septum aorto-pulmonalis now invades the portion of the truncus which lies within the pericardial sac and adds itself to the factors producing a separation between the two vessels. We now have the two sets of ridges, *A* and *B*, and 1, 2, 3 and 4, and the septum aorto-pulmonalis. This septum pushes forward its two horns which thus enclose between them a free sickle-shaped edge and finally effects a junction with ridges 1 and 3, which in turn becomes continuous with ridges *A* and *B*. The process thus initiated progresses slowly, the sickle-shaped free margin passes caudally. The ridges become thicker and thicker until they fuse from above downward and the two vessels become completely separated. Through the spiral arrangement of the ridges we now have two curving tubes which looked at from above present a pulmonary artery passing forward and to the right, and an aorta passing posteriorly and to the left closely applied and wrapped about one another.

At a somewhat later time the vessels become independent through their separation by the external furrows which corresponded to the internal ridges. Having now seen the single trunk divided into two separate vessels, we can follow the development of the semilunar valves. Through the fusion of ridges 1 and 3 each vessel contains one half of each fused ridge and in addition the smaller ridge which lies between the larger ridges. The aorta contains ridge 2, the pulmonary artery ridge 4; these smaller ridges fade away distally but in the region of the junction with the ventricle they enlarge and become hollowed out, forming one of the semilunar valves; the other two valves are formed through similar processes taking place in the halves of ridges 1 and 3 left in each vessel.

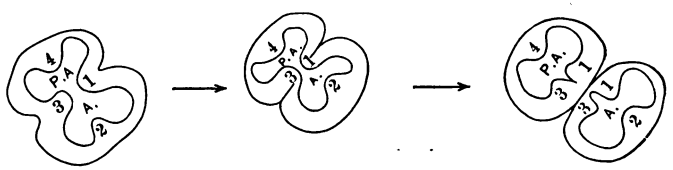
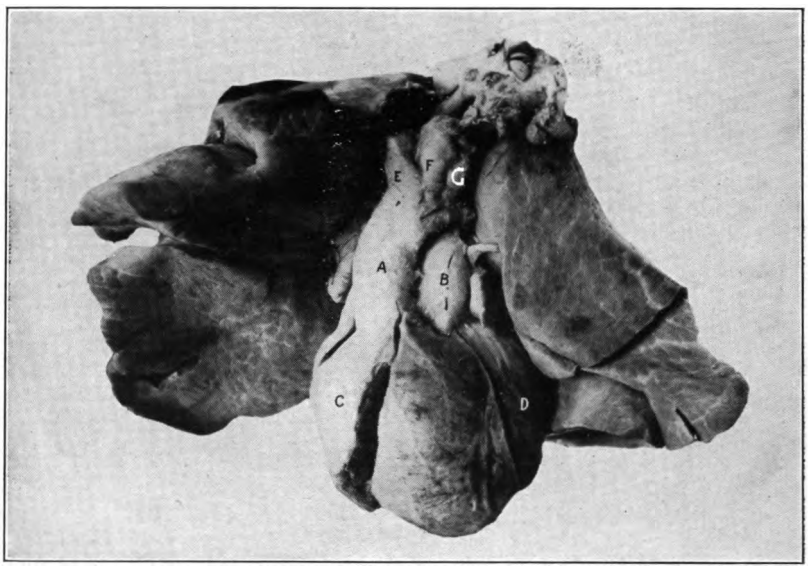


Diagram to illustrate the formation of the semilunar valves which develop by the hollowing out of the lowermost extremities of the ridges 1, 2, 3 and 4. The diagram also illustrates how ridges 1 and 3 participate in the formation of valve-flaps in both the aorta and pulmonary artery.

The two vessels now open into the ventricle which has become divided by the interventricular septum into the smaller right and the larger left half. This septum grows up from the floor and both anterior and posterior walls at the same time so that it presents two horns, an anterior and a posterior, containing between them a free sickle-shaped border. Meanwhile, the most inferior portions of ridges *A* and *B* have grown forward, joined, and have produced what we call the proximal bulb septum. Viewing this from above, we find that it passes from the right superiorly and posteriorly toward the

left anteriorly and inferiorly, and thus sets itself in a warped fashion on the interventricular septum which is growing upward to fuse with it.

The anterior cornu of the septum trunci fuses with the anterior horn of the interventricular septum, while the posterior cornu of the septum trunci spreads out on the posterior ventricular wall and fuses with the right extremity of the posterior endocardial cushion of the atrio-ventricular canal. If we follow the boundaries of the interventricular foramen, we now find them as follows: starting from above and behind we have the warped under surface of the septum trunci leading to the anterior cornu of the interventricular septum, advancing downward along the anterior wall to the inferior sickle-shaped intercornual margin, back and finally upward along the poste-



Photographs of the specimens embodied in the report.

FIG. 4. Complete transposition of the arterial trunks. *a*, aorta; *b*, pulmonary artery; *c*, right ventricle; *d*, left ventricle; *e*, innominate artery; *f*, carotid artery left; *g*, left subclavian.

rior cornu of the septum to the right extremity of the posterior endocardial cushion. This space is gradually closed in by downgrowth of the septum trunci and upgrowth of the interventricular septum until they meet and fuse.

As a result of the direction of the septum trunci toward the right end of the posterior endocardial cushion, we find the right atrio-ventricular opening close to the septum, the left separated from it by some distance.

Having seen the mechanism by which the great vessels become separated from one another, it is a comparatively easy matter to see how readily anoma-

lies of the arrangement of the great vessels may occur. Rokitansky, in his schema of the rotation of the great vessels, distinguishes two main groups according to whether the transposition was corrected or not with eight subdivisions in each group, the subdivisions being stages in the spiral twist and the form that the transposition would take in each subdivision were the spiral arrested at that point. In his schema *A* we find the transposition is corrected, for, in spite of the altered relation between the two great trunks, they are connected with the proper ventricle by a compensatory twist of the interventricular septum. In schema *B* we find, however, a true transposition of the trunks, there having been no correction and the trunks being connected with the wrong ventricle. The behavior of the interventricular septum determines whether correction takes place or not.

Partial Transposition.—This is relatively infrequent, but it exists and results in the large vessels arising from the same or a common ventricle and is due to the application of the interventricular septum to either one side or the other of the large vessels instead of between them. In such cases it is the rule to find the orifice of one or the other of the vessels encroached upon.

An anomalous septum may cut off an abnormal cavity as an origin for the two vessels. Unless some other anomaly is present and persists, complete transposition is incompatible with life, for we have the lesser circulation cut off and transformed into a closed circulation. This deprives the blood of any opportunity to gain access to the greater circulation unless it is by some abnormal channel as a patent ductus, a patent foramen ovale or a defect in the interventricular septum; correspondingly, the blood in the greater circulation fails to gain access to the lungs.

Defects of the Interventricular Septum.—As is usually the case with cardiac lesions, we often find other lesions associated with defects in the interventricular septum, the great vessels being often affected. This is readily understandable when we consider the close relationship between the two sets of structures.

Types: (*a*) Complete.
(*b*) Incomplete.

If complete we may find either a condition known as cor triloculare biatriatum or cor biloculare, depending upon the presence or absence of the interauricular septum. In association with the latter we may find a common auriculo-ventricular orifice and an undivided truncus.

These defects may be viewed mainly as arrests of development and in the majority of cases may be explained by a simple schema of the development of the interventricular septum. The septum develops from four component parts:

(*a*) The proximal septum trunci.
(*b*) The anterior horn of the interventricular septum.
(*c*) The posterior horn of the interventricular septum.
(*d*) The intercornual septum.

(*a*) Defects in the septum due to faulty development of the septum trunci constitute the most frequent type. The defect is located close under the orifices of the great vessels and occupies the area known as the "undefended space" or the pars membranacea.

(*b*) Defects due to the failure to develop of the anterior horn of the interventricular septum are located in front of the pars membranacea.

(*c*) Defects due to failure to develop in the posterior horn are correspondingly located behind the pars membranacea.

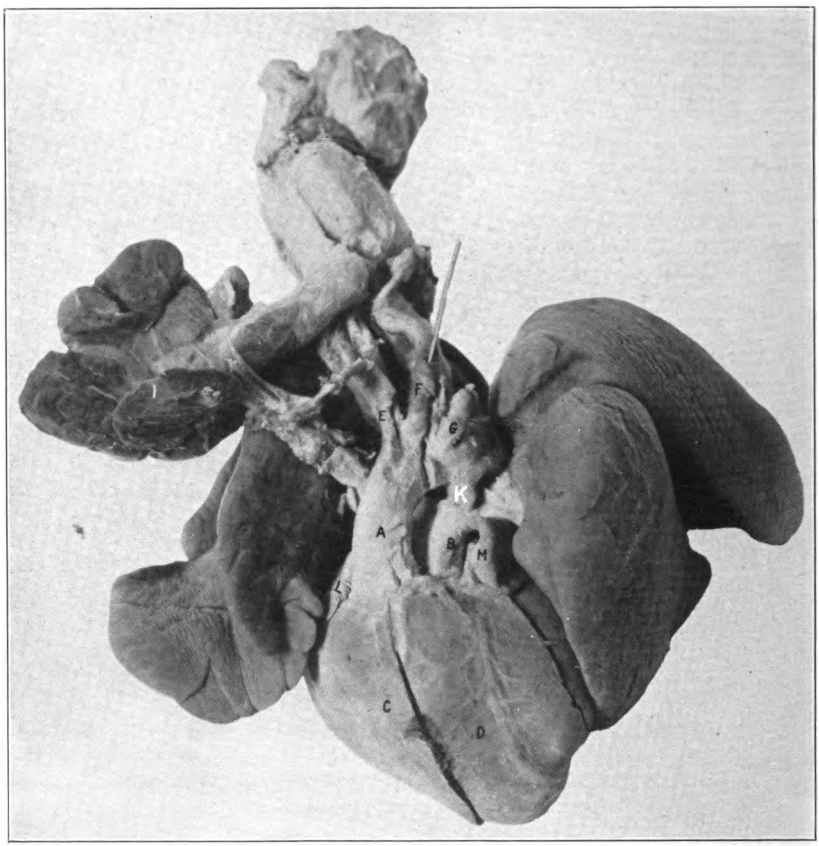


FIG. 5. Complete transposition of the arterial trunks. *a*, aorta; *b*, pulmonary artery; *c*, right ventricle; *d*, left ventricle; *e*, innominate artery; *f*, left carotid artery; *g*, left subclavian; *k*, ductus arteriosus; *i*, thymus; *l*, right auricle; *m*, left auricle.

(*d*) Defects due to faulty development of the intercornual portion may lie at any point in the septum, but they are more usually close up under the pars membranacea and are due to failure of the two septa to join.

COMPLETE ABSENCE OF THE INTERVENTRICULAR SEPTUM

CASE II. *Pathology.*—Externally the heart is quite normal in shape. It weighs 170 grams, measures $8 \times 7.5 \times 6$ cm., and has a fairly well defined and formed apex. There is, however, no interventricular groove to be seen and no indication of any division into two ventricles. The great vessels appear to arise from the heart on almost the same plane; the aorta from the right side,

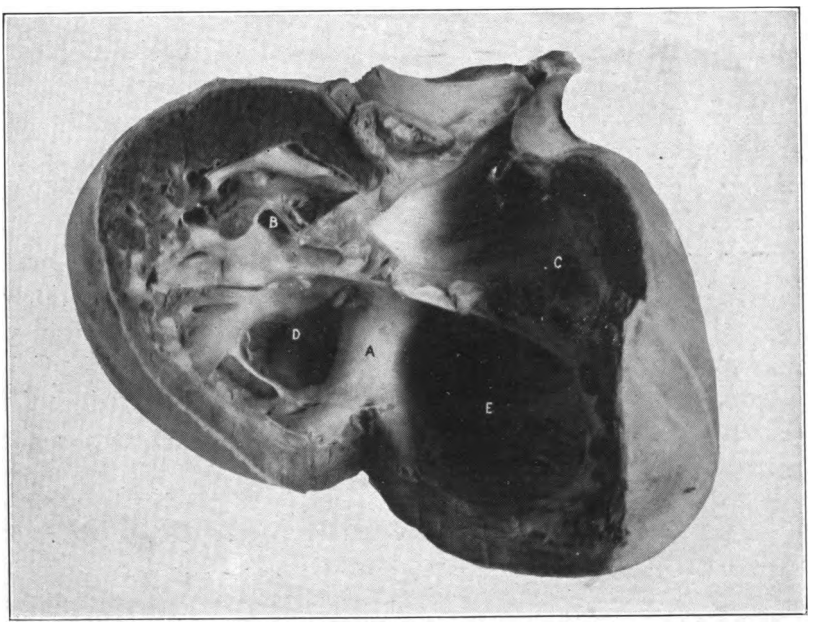


FIG. 6. Cor triloculare biatriatum. *a*, septum trunci; *b*, left auricle; *c*, right auricle; *d*, left ventricular portion of common ventricle; *e*, right ventricular portion of common ventricle.

the pulmonary artery from the left and slightly posterior so that we have here also a case of transposition of the vessels. The vessels are cut off so close to the heart that their further course cannot be followed but so far as we can see there is no indication of any ductus. Upon opening the auricles, we find that the right auricle is the larger, the right auriculo-ventricular orifice measuring 5 cm. in circumference; the left auricle is smaller, its auriculo-

ventricular orifice being 3 cm. in circumference. A rough estimate of the capacities of the two auricles would make that of the right three times that of the left. The right valve presents three flaps and several thickenings varying from 1 to 6 mm. in size. The left valve presents two main flaps which are broken up into a number of smaller ones by the insertion of anomalous chordæ tendineæ. The interauricular septum forms a common site of origin for both valves and a common papillary muscle receives chordæ from each of these valves.

There is but a single ventricle without any evidence of attempt at division in two by an interventricular septum. The walls are thick and heavy and present large papillary muscles and columnæ carneæ. The auriculo-ventricular orifices present at the posterior part of the ventricle, the orifices of the great vessels at the anterior part of the ventricle, the aortic on the right, the pulmonary on the left. These orifices are separated by a thick, heavy band of muscle fibers passing anteriorly and posteriorly between them and represent the proximal septum trunci.

I am much indebted to the anatomical department of the College of Physicians and Surgeons for permission to reproduce the reconstructions indicating the divisions of the truncus into the aorta and the pulmonary artery.

ADDITIONAL CASE REPORT

Since the report of the preceding case of complete transposition of the arterial trunks, it has been our good fortune to find another instance of the same pathological condition. The two hearts are almost identical and present pictures that agree in every essential point. In the second instance the child lived for about six hours after birth. There was a great deal of cyanosis affecting particularly the extremities, the hands and feet being a deep indigo.

Upon opening the thorax the organs were found to be intensely engorged and congested, the lungs being almost black. As soon as the pericardium was opened, the transposition was recognized and the organs were removed *in toto*. As in the previous case the aorta arises from the right ventricle, passes upward, giving off the great vessels from its convexity and receiving on its concavity the patent ductus arteriosus as it passes over the pulmonary artery. The pulmonary artery shows the same arrangement as we have seen previously, dividing into its two pulmonary arteries under cover of the aortic arch, the left one in turn giving off immediately the ductus arteriosus.

Upon opening the right auricle, it is found to be large and dilated; the

foramen ovale is patent along its anterior edge. The left auricle is considerably smaller than the right. The right ventricle presents the origin of the aorta. Passing posteriorly and slightly to the right behind the origin of the aorta is a thick heavy band of muscle fibers which represents the lower margin of the primitive septum trunci. It serves to separate the aorta and the right auricle and from its posterior aspect it gives origin to one of the flaps of the tricuspid valve. The origin of the two coronary arteries can be seen in the posterior and left sinuses of Valsalva of the aorta. The flaps of the mitral and tricuspid valves are normal in structure and number. The left ventricle presents the origin of the pulmonary artery arising anteriorly and close to the interventricular septum. The interventricular septum presents no defects.

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Discussion:

DR. MACCALLUM: I think Dr. Riley has covered the ground pretty thoroughly. There is one striking point in this connection and that is the mathematical regularity with which certain principles are carried out in transpositions of the great vessels. In making out his schema Rokitansky was able to prophesy anomalies of the great vessels and several types which had not been reported prior to this, but which he had figured as possible in his schema were later reported by different observers. A good deal of light can be thrown on this subject by cutting the hearts transversely close under the great vessels to show the disposition of the aortic and interventricular septa and by comparing them with pathological hearts cut in a similar fashion. A better idea of the relationships can be gathered in this fashion than by cutting the heart in the usual fashion through the valve flaps.

DR. LARKIN: I have had rather an interesting anomaly of the heart recently. The child had spina bifida. In these cases anomalies of the cardia are not infrequent. The child presented several abnormal conditions. This abnormality of the heart has never before been described. The charts of Dr. Riley give an idea of the disposition of the vessels. In my case the aorta leads directly into the right and also into the left ventricle, the pulmonary artery being normal. The aorta is normal until the base of the heart, where there is a lack of the septum. The aorta is bifurcating, one part goes to the right ventricle, one to the left.

DR. RILEY: The explanation is I think that the interventricular septum comes up from below and the septum trunci comes from above; they do not meet and the interventricular septum separates the aorta into two parts.

DR. LARKIN: There is no evidence of any upper septum at all.

DR. RILEY: You have a division of the truncus into two vessels.

DR. LARKIN: The pulmonary goes into the right ventricle, the aorta into the left. There is no abnormality of the pulmonary.

FIVE CASES OF PRIMARY CARCINOMA OF THE APPENDIX

A. B. EISENBREY, M.D.

(From the Pathological Department of St. Luke's Hospital, F. C. Wood, Director)

The five cases of primary carcinoma of the appendix to be reported were found among approximately eighteen hundred appendices examined in the pathological laboratory of St. Luke's Hospital during the past three years. The incidence of this lesion among our cases is thus seen to be 0.3 per cent. as contrasted with the 0.4 per cent. and 0.5 per cent. reported by other observers. Four of the five cases were females and the ages of the patients varied from nineteen to sixty years. In one of the cases the lesion was found at autopsy, and in but one of the remaining four cases was attention directed to the appendix before operation. In two instances only was the presence of carcinoma suspected from the gross appearance. In two of the appendices the lesion was situated in definite thickened areas at about the mid-point in the organ; in two others it was found in the enlarged clubbed tip, and in the fifth in the constricted fibrosed tip. In none of the cases was there macroscopical evidence of extension through the serous coat of the organ, nor was the organ adherent to the surrounding structures; no other carcinomatous lesion was found elsewhere in the body, either at operation or at autopsy. The appendices ranged from 4.5 cm. to 6 cm. in length and from 0.5 cm. to 1 cm. in diameter, except at the site of the lesions, of which the largest was 1.2 cm. in diameter.

Microscopically the lesions all showed the most frequently described type of appendiceal carcinoma: destruction and replacement of glandular and lymphoid structures by a rather dense fibrous stroma, supporting islands and strands of cells of the spheroidal epithelial type which also invaded the muscularis and in several of the cases were found in the subserous structures. In two of the cases the cells were smaller, fewer large islands were found and the growth in general was of a more scirrhus type.

(We had a sixth case of carcinoma of the appendix which is not included in this report. It was of the gelatinous type and while the chief growth and origin appeared to be in the appendix the cæcum was also extensively involved so that it is not justifiable to class it as primary in the appendix.)

CASE I. (Path. No. 8084.) Female, aged twenty-five, gave a history of pelvic disturbances following birth of child six and a half years before but showed no symptoms referable to the appendix. At operation for the correction of retroversion of the uterus the appendix was found to be constricted at the distal fifth of its length and was removed. The carcinomatous growth was seen, in longitudinal section of the constricted portion, to involve the area nearest the base where its relation to the mucosa was well shown. The region of the tip was free from the growth. The islands of cells in this case were large with rather large and vesicular cells.

CASE II. (Path. No. 8415.) Male, aged sixty, was operated upon for acute appendicitis of three days duration. He gave no history of any previous disturbances of like nature. At operation the appendix gave evidences of a chronic inflammatory process with an added acute congestion. The middle portion of the organ was slightly thickened and densely fibrosed. The cells were of a smaller type, the islands small but numerous, with a well marked invasion of muscularis and subserosa.

CASE III. (Path. No. 10845.) Female, aged thirty-one, gave a history of symptoms referable to the pelvic organs, extending over a period of five years. No symptoms were directly referable to the appendix. At operation for double salpingitis and retroverted uterus the appendix was found thickened throughout, the serosa was congested but smooth, and there was considerable clubbing of the tip. In this case the cells were of the large clear type, the cell nests large, and the invasion of the subserosa most marked.

CASE IV. (Path. No. 11554.) Female, aged forty-two, was operated upon for fibromyomata of the uterus and the appendix removed incidentally. There was marked clubbing of the tip and considerable congestion and a slight exudate on the serosa

over it. The lesion was well confined to the region of the mucosa and submucosa. The cells and cell-groups were of the large type.

CASE V. (Autopsy No. 1153.) Female, aged nineteen, died of septicæmia following a septic endocarditis of probable rheumatic origin. The appendix appeared normal externally except for a hard thickening about 1 cm. in diameter at its middle. On section this was of dense fibrous structure with a rather granular surface of yellowish color, an appearance noted in the other cases of this series which we believe characteristic of this type of lesion. In this case the growth was of the scirrhus type, the cells were small and the invasion to the serosa well marked.

Discussion:

DR. EWING: In connection with reports of cases of carcinoma of the appendix it has been objected that while these processes have the morphology of carcinoma they are not genuine malignant tumors, but merely atypical overgrowth of aberrant epithelial rests or of displaced portions of mucosa which possess a very limited power of proliferation. Many of the cases fail to show the clinical features of a malignant tumor and it may well be that some of the tumors are practically at a standstill when observed. I think, however, that they are properly regarded as true carcinomas of their own peculiar sort. We have no right to demand that they should show all the characteristics of malignant tumors in other parts of the body. They most resemble the basal cell carcinomas.

DR. EISENBREY: There are mitotic figures in these specimens, but they are hard to find. In none of the cases were there enlarged glands of the mesoappendix, nor was there any demonstrable carcinoma elsewhere, except in the case of gelatinous carcinoma, where the cæcum was also involved. That case is not included in this series.

DR. PAPPENHEIMER: Are there any cases in the literature in which widespread metastases have been reported?

DR. EISENBREY: Yes, there are some cases where there is active recurrence. So far as this particular type goes, I do not believe there are any recurrences.

EXTRA-MEDULLARY MYELOID CHANGES IN ORGANS

W. G. MACCALLUM, M.D.

Dr. MacCallum presented preparations from two cases to illustrate the appearance of myeloid tissue in organs other than the bone marrow. One of these was a case of so-called osteosclerotic anæmia in which the destruction of practically all of the bone marrow by metastases from a carcinoma of the prostate resulted in an extreme anæmia and the spleen and liver were found laden with myeloid cells. The venules of the spleen were especially filled with myelocytes. The second case was one of myeloid leukæmia in which distinct nodules of myeloid tissue including megalocaryocytes were found in the liver. Two views have been held as to the origin of these cells; one being that elements originally present in most tissues and capable of production of cells of the blood are reformed by a sort of reversion to embryonic conditions; the other being that myeloid cells are swept out of the bone marrow and in case of necessity colonize in other organs and there produce the elements of the blood. In the case demonstrated the latter view seems most probable.

Discussion:

DR. PAPPENHEIMER: I would like to ask whether, in the case of extreme sclerotic anemia, any myeloid cells found their way into the circulation.

DR. MACCALLUM: There were foci of the same sort. I don't believe any went into the circulating blood. There were some in the adrenals.

DR. FIELD: These myeloid changes are very frequently found in areas of arterio-sclerosis in the aorta, in cases which have shown only slight anemia. It would seem to me that Maximow's *Wanderzellen* can give rise to both series of blood cells when the nutritive and pressure conditions are favorable, in the same way as they do in embryonal life.

DR. EWING: Does Dr. MacCallum know of any definite instance in pathology where an embryonal function or tissue, once passed through its normal course of development to the adult, experiences a reversion to the embryonal condition?

Dr. MacCallum was glad that Dr. Ewing expressed himself as opposed to the idea of a reversion of cells to embryonic form and function, since he had seen no evidence of it. The explanation is difficult in the case of bone marrow formed in necrotic tissue found in the walls of blood vessels and the lung, but in other cases the theory of colonization seems better supported.

LATE RESULTS IN ACTIVE IMMUNIZATION WITH DIPHTHERIA TOXIN–ANTITOXIN AND WITH TOXIN–ANTITOXIN COMBINED WITH DIPHTHERIA BACILLI

WM. H. PARK, M.D., AND ABRAHAM ZINGHER, M.D.

(From the Research Laboratory and the Willard Parker Hospital, Department of Health, New York City)

The property of diphtheria toxin-antitoxin mixtures to produce immunity in animals has been known for a number of years, but its application to human beings was not practised until Von Behring recommended it in May, 1913. The early reports of Von Behring and his co-workers were so favorable that we determined to make a similar attempt at the Willard Parker Hospital.

Several series of patients were injected with mixtures of diphtheria toxin and antitoxin, in such proportion that the mixture was either overneutralized, just neutral or slightly toxic to the guinea-pig. In the last series of cases (Group III) we used a mixture consisting of 85 per cent. of the L_+ dose of toxin to each unit of antitoxin, to which was added a vaccine made from killed diphtheria bacilli.

In a previous communication we published the following conclusions, derived from the results obtained in the immunization of two groups of scarlet fever patients who were injected with toxin-antitoxin:

1. Those who had a natural antitoxic immunity produced a decided increase in the amount of antitoxin in a short time (seven days), even after a single injection of toxin-antitoxin.

2. Those who had no natural antitoxic immunity were quite resistant to active immunization. Only 25–30 per cent. showed decided antitoxin production within four to six weeks after injections of toxin-antitoxin. A larger proportion produced a trace of antitoxin, and gave a fainter Schick reaction than in the original test. The reaction was still positive, however, and they were not considered immune.

3. We concluded, therefore, that toxin-antitoxin could be used

where no immediate danger of infection was present. Non-immune individuals exposed to diphtheria, however, should be protected with antitoxin.

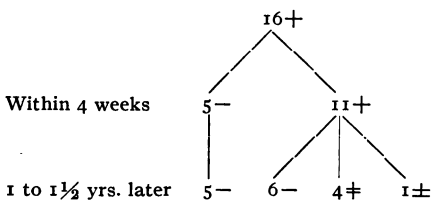
Observations on our chronic tube cases, who developed slowly, but almost uniformly, an antitoxic immunity, led us to retest with the Schick reaction those who were at first partially or totally refractory to immunization with toxin-antitoxin.

From Group II (toxin-antitoxin) we retested sixteen cases, from Group III (toxin-antitoxin plus bacterial vaccines) fifty cases, at intervals of from two months to one and one-half years after the immunizing injections.

In Group II, a series of ninety patients was originally injected who had no natural immunity, as shown by blood examination for antitoxin and by a positive Schick reaction. Of the ninety, twenty responded to the injection of toxin-antitoxin with the production of sufficient antitoxin to protect against diphtheria; seventy failed to respond to this degree, though some gave a fainter Schick reaction than they had shown before the immunization. Among the twenty no cases of diphtheria developed; of the seventy who produced very little or no antitoxin, seventeen developed clinical diphtheria twelve days and more after the first injection.

From Group II, sixteen cases were subsequently retested one to one and one-half years after the injections of toxin-antitoxin.

EARLY AND LATE SCHICK TESTS IN GROUP II.



— indicates negative Schick reaction.
∓ indicates faint Schick reaction.
± indicates moderate Schick reaction.
+ indicates fully developed Schick reaction.

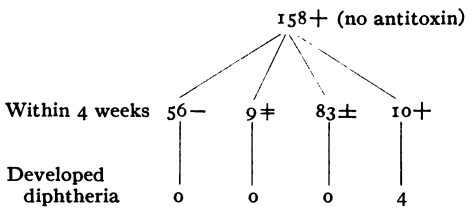
Five of the sixteen who had shown an early and decided production of antitoxin, again gave a negative Schick reaction. Of the eleven who had failed to respond at first to the immunizing injections, six now gave a negative, four a very faint and only one a positive Schick reaction.

Group III consisted of one hundred and fifty-eight patients, who had originally given a positive Schick reaction. These patients were immunized with a mixture of toxin-antitoxin and a vaccine made of killed diphtheria bacilli. Three to four subcutaneous injections were given at intervals of three to four days, each injection consisting of 1 c.c. toxin-antitoxin (85 per cent. L_+ dose of toxin to each unit of antitoxin), and 1,000,000,000 bacteria. One c.c. of the mixture injected subcutaneously into a guinea-pig produced a slight local induration and paralysis in ten days.

EARLY RESULTS IN GROUP III

158 cases

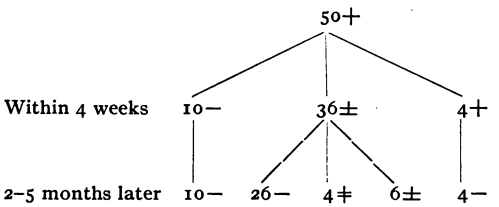
No antitoxin (+ Schick) before immunization



Of the one hundred and fifty-eight injected patients, fifty-six or 35.5 per cent. produced enough antitoxin within four weeks to give a negative, and nine, or 6 per cent., a very faint Schick reaction. Of those who were partly or totally refractory, eighty-three, or 52 per cent., gave a moderately positive, and ten, or 6.5 per cent., a strongly positive Schick reaction. Of the ten, four developed clinical diphtheria.

To note any late development of immunity, we retested from two to five months after the injections, fifty cases of this group.

EARLY AND LATE SCHICK TESTS IN GROUP III.

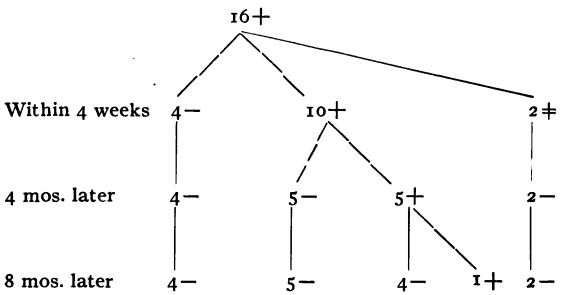


Ten of the patients who had given a definite early production of antitoxin continued to show a negative Schick reaction. Of the thirty-six patients who had produced only a trace of antitoxin, not sufficient to inhibit the Schick reaction, twenty-six now gave a negative, four a very faint and six a moderately positive reaction. The remaining four who were refractory at first, now gave a negative Schick reaction.

Grouping together the early and late successful results in this series of cases, we find that forty out of fifty susceptible individuals had developed an antitoxic immunity after the injections of toxin-antitoxin plus vaccine. The remaining ten gave a reaction which was moderately positive in six and faintly positive in four cases. These cases probably had developed some bactericidal immunity from the bacilli injected.

In addition to these, we also immunized with toxin-antitoxin, a series of sixteen normal children (Group IV), who had given a positive Schick reaction. These children were injected about a year ago, and retested with the Schick reaction four and eight months after the immunization.

EARLY AND LATE SCHICK TESTS IN GROUP IV (NORMAL CHILDREN)



Within four weeks after the injections, only four, or 25 per cent., gave a negative Schick test. Four and eight months later, these four still gave a negative reaction, thus indicating a probable lasting immunity. Ten children, who were refractory at first, now showed the following interesting results: at the end of four months, five gave a negative and five a positive Schick reaction. At the end of eight months, nine showed a negative reaction and only one was still positive. Two of the sixteen children who had given a partial early response, were found immune at the end of four and eight months.

As control, we had a group of six children who had received antitoxin only a year ago. At the end of eight months, five of the children still gave a positive Schick reaction, and one only had now become negative.

Another group that may serve as control consisted of sixty children who had received vaccines made only from diphtheria bacilli. Retested from five to eight months after the injections, forty gave a positive and twenty a negative Schick reaction.

Our results in active immunization up to the present time have led us to the conclusion that, while the toxin-antitoxin injections cannot be depended on to prevent diphtheria in the presence of immediate danger of infection because of the slow development of immunity in a majority of the cases, yet the injection is of value in rendering a community or school population immune to the danger of infection from future exposure up to a period of possibly several years.

CONCLUSIONS

1. Individuals who before treatment give a negative Schick reaction are immune probably for life, and therefore it is not necessary to inject them either with antitoxin or toxin-antitoxin.

2. Those who give a positive Schick reaction and are exposed to diphtheria and in immediate danger, should receive either antitoxin alone, or if a longer protection is desired, both antitoxin and toxin-antitoxin.

3. For general prophylaxis against diphtheria excluding im-

mediate contacts, a mixture of toxin-antitoxin alone (85–90 per cent. of the L_+ dose of toxin to each unit of antitoxin) or toxin-antitoxin plus vaccine of killed diphtheria bacilli, is recommended. The dose is 1 c.c. of toxin-antitoxin and 1,000,000,000 bacteria injected subcutaneously and repeated three times at intervals of six or seven days. Sufficient time has not yet elapsed to judge the value of adding the injections of the bacilli to the toxin-antitoxin.

4. The early and the late results of active immunization should be determined with the Schick test. Early results are those obtained by the application of the test within four weeks, late results from four months to two years after the immunizing injections.

Discussion:

DR. FIELD: Dr. Zingher's paper is extremely interesting in that it gives us an explanation from the laboratory as to why diphtheria is a disease of the younger years and is comparatively rare among adults. When we realize that 5 per cent. of all school children harbor the diphtheria bacillus in their throats, it is readily understood why such a large proportion should be found to be immune by the Schick test.

DR. ZINSSER: The antitoxin contents of the blood are relatively high during the first year of life, then lower, again increased toward adult life, falling again in old age.

DR. FIELD: It falls in with the Schick test.

DR. ZINSSER: An interesting point in Drs. Park and Zingher's paper is that they are using mixtures which are not over-neutralized, namely, an L_+ dose with one unit. In Behring's experiments I believe the mixtures were considerably over-neutralized.

DR. FIELD: In regard to the production of antibodies by mixtures of toxin and antitoxin, I would like to call the attention of the Society to the fact that Dr. Park reported on this point before the Society fourteen years ago. The work had been done two or three years previous to his making the report, and when Ehrlich visited the Research Laboratories he was surprised to discover this point; I well remember his animated conversation with Dr. Park in regard to it.

DR. ZINGHER: Antitoxin production is abundant in the horse after injections of neutralized or over-neutralized mixtures of diphtheria toxin and antitoxin. Similar results are obtained in human beings who are naturally immune. There is probably a dissociation of the toxin-antitoxin mixture *in vivo*, and a ready response of the tissue cells to the antigen. It is important to have the right proportion of toxin and antitoxin in the mixtures used for active immunization. A mixture that is only slightly toxic to the guinea pig gives the most satisfactory results in non-immunes. Von Behring did not

give in detail the exact proportions of toxin and antitoxin. He injected neutral and slightly toxic mixtures. The doses he recommended were only a fraction of the ones we used.

DR. ZINSSER: We are learning all the time that we can immunize with antigen-antibody combinations in which apparently no free antigen is present. This is, of course, the principle underlying immunization with sensitized vaccines as introduced by Besredka and the early experiments of Kraus and others on protection with sensitized cholera spirilla. It seems hard to understand this unless we assume dissociation of the antigen-antibody complex within the body.

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CONTENTS

FOUR CASES OF PRIMARY CARCINOMA OF THE LUNG

ROBERT A. LAMBERT, M.D.

(From the Pathological Laboratory of Montefiore Hospital, New York City)

The relative infrequency of primary carcinoma of the lung is the reason for bringing before the Society four specimens which were encountered among less than fifty autopsies performed at Montefiore Hospital during the past eight months. Such a high incidence is very unusual and is undoubtedly accidental, in view of the reports of incidence of 0.2 to 1.0 per cent. from many other institutions. A review of Dr. Adler's excellent monograph on "Primary Malignant Growths of the Lungs and Bronchi," in which all of the published cases have been collected, has convinced me that our four cases belong to well recognized types of lung carcinoma. The first two are distinct squamous

celled epitheliomata, prickle cells and keratinizing "pearls" being frequently encountered. The third belongs to the group of adenocarcinomata arising in bronchial glands. The cells exhibit in many places an active secretion of mucus. The fourth is a papillary adenocarcinoma, the cells of which possess in places definite cilia.

An interesting feature of these cases is the difference in the tendency toward metastasis formation. The first two tumors showed no metastases. The third, on the other hand, besides an extensive local spreading, metastasized to the axillary, cervical and abdominal lymph nodes, and liver; while in the fourth case, a papillary ciliated epithelial tumor, metastatic nodules were present, not only in most of the abdominal viscera, but also in various bones (vertebræ and ribs especially) and in the brain.

The squamous cells of the first two tumors, which are generally thought to arise from the cylindrical epithelium of the bronchi, must be regarded as having strayed far from the parent type; that is, the cells are, in this sense, very atypical. Yet, in their behaviour they appeared less malignant than the more nearly typical cells of the third and fourth cases. Indeed, it was the ciliated epithelial cells of the last case that manifested the most pronounced tendency to metastasize.

Complete reports of these cases will be published elsewhere.

Discussion:

DR. NORRIS: I was greatly interested in Dr. Lambert's presentation. He has been very fortunate in finding four cases of primary carcinoma of the lung in such a small series of autopsies. At Bellevue we have records of approximately 4,800 autopsies, and I have seen but two cases of supposed primary tumor of the lung. One of these cases occurred in October, 1904. Recently in looking over the records of primary carcinomas of the lungs, the protocol of the case does not mention the condition of the œsophagus. The tumor was a frank epithelioma. I question very much that the case represents a true primary epithelioma or carcinoma of the lung. The second case occurred more recently. There was a large tumor mass at the hylus of the lung, involving the bronchial and tracheal lymph nodes; there were no metastases with the exception of a small nodule in the small intestines. The microscopic picture in both cases was similar, namely, the tumor was acinous in structure with production of mucus. I do not feel sure that the small

nodule in the intestine was not the primary seat of the growth. This autopsy was done very carefully and it was thoroughly sifted.

DR. SCHULTZE: I held an autopsy on one of Dr. Adler's cases where there was a terminal hæmorrhage. I took issue with the doctor as to its being an endothelioma. I considered the case one of carcinoma of the lung. Since then I have seen two cases which may be primary endothelioma. One started in the bronchial lymph nodes with metastases into the bone marrow. Probably both types of tumors exist.

DR. LAMBERT: I think Dr. Norris's criticism is pertinent. It is possible that one of these cases may not be primary in the lung. There was a small erosion of the œsophagus. But I do not think the tumor could have been an œsophageal growth. It would be remarkable for a tumor of the œsophagus to infiltrate the lung as extensively as this one did. I do not think there is any doubt about the other three tumors being primary in the lung. The autopsy was complete in each case and a careful search was made for other possible sites of origin.

REPORT OF AN UNUSUAL CASE, PRESENTING PRIMARY, MULTIPLE, BENIGN, MEDULLARY, GIANT-CELL BONE TUMORS

H. S. MARTLAND, M.D.

(*From the Pathological Laboratory, Newark City Hospital*)

Introduction

Sarcomata occurring in or near the ends of long bones, endosteal, medullary or myeloid in character, and showing a microscopical picture characterized by numerous giant-cells, having abundant, dark staining and often vacuolated cytoplasm, numerous and regular nuclei with absence of mitotic figures, and a stroma consisting of fibroblastic granulation tissue without active mitoses, dilated and engorged blood-vessels, hemorrhage in perivascular tissue, erosion and disintegration of bone trabeculae, have been recognized for many years under such terms as medullary or myelogenous giant-cell sarcomata.

Adami and Bland Sutton have objected to their classification as sarcomata on the grounds that the type of giant-cell en-

countered in this tumor is a cell resembling the osteoclast or myeloplax occurring in normal bone marrow, and also, from the well known clinical fact, that these tumors were much less malignant than periosteal sarcomata, and in many cases distinctly benign.

Bloodgood, in 1902, was the first in this country to seriously study this tumor, and he concluded that he did not believe that this type of tumor ever caused metastases, but would recur *in loco* when not thoroughly removed, a fact that was recognized as early as 1895, by Koenig, Bergmann and Mikulicz. Bloodgood therefore concluded that it was not a sarcoma, and for a better name. termed it medullary giant-cell tumor.

Mallory considers the giant-cells encountered in this tumor as foreign-body giant-cells, formed by the fusion of endothelial leucocytes, and believes that in forming a diagnosis, they should be considered as entirely of secondary value. Mallory would attempt to trace the tumor back to its type cell, say the fibroblast, and the tumor's malignancy would be determined by the presence or absence of active mitosis.

Barrie, in 1913, called attention to the characteristic macroscopic and microscopic appearances of these tumors, which are entirely different from that of malignant periosteal tumors. Barrie believes that the process is not a tumor formation at all, but merely a chronic non-suppurating form of osteomyelitis, therefore he has named the lesion chronic non-suppurative hemorrhagic osteomyelitis.

The table below gives a condensed idea of the clinical and pathological facts known, in so-called medullary giant-cell sarcoma or chronic hemorrhagic osteomyelitis of Barrie.

CLINICAL FACTS.

Situation: Ends of long bones, especially upper end of tibia.
Trauma: Definite history in large majority of cases.
Age: Young people, large majority.
Onset: Usually sudden.
Malignancy: Will recur *in loco* after incomplete removal, but will never form metastases.

Roentgenograms: Expansive, abrupt and circumscribed tumors; distention may be great, bone shell preserved.

PATHOLOGICAL FACTS.

Gross Appearance: Tumors usually confined within periosteum. Definitely circumscribed, not infiltrating. Easily removed from bone shell. Are distinctly vascular, resembling young granulation tissue, friable, soft and ooze. Resemble currant-jelly or fresh cut liver. Later this picture may change, and the tumor become cystic.

Microscopic Appearance: Giant-cells of foreign-body or osteoclastic type.

Nuclei: Regular in size and shape. Numerous. Absence of mitotic figures.

Cytoplasm: Dark staining. Abundant and often vacuolated.

Stroma of Tumor: Suggests young granulation tissue, with endothelial-lined blood-spaces separated by connective tissue stroma, filled with spindle and round cells, showing few if any mitotic figures.

I wish to present the histories, clinical courses, and pathological findings in two cases presenting bone tumors of the above described type. Both patients are from the surgical service of Dr. F. R. Haussling at the Newark City Hospital.

The first case presents an expansive tumor involving the lower end of the right tibia, of over eight years' duration, which on microscopical examination shows the typical picture of the so-called medullary giant-cell sarcoma. I present this case to demonstrate the benign character of this well-known tumor.

The second case presents multiple expansive bone tumors, the clinical picture resembling that of multiple myeloma; the microscopical appearance of the tumors, however, is that of the so-called medullary giant-cell sarcoma. Multiple tumors presenting this microscopical appearance have hitherto been undescribed.

CASE I. *History:* A. L. Male, Italian; age twenty-eight years; barber. Past history: Had chancre when eighteen years old. In 1907, he twisted his right ankle while playing ball; leg was put in plaster three weeks; he then received luetic treatment for one month; plaster cast again applied for two months; lower end of tibia curetted, and after wound healed he was discharged as cured. In 1908, the swelling and pain returned in the ankle; the tibia was again curetted, a diagnosis of osteomyelitis made and he was discharged with a persistent sinus. In 1910, he fell and again injured ankle; he was at this time admitted to the City Hospital. Subsequent history: The lower end of the tibia was curetted, and microscopical examination showed myelogenous giant-cell sarcoma. The wound healed, but old sinus persisted. During 1911, the tibia was curetted four times for recurrence. In 1915, the tibia was again curetted for recurrence in and about sinus, and the surgeon noted that the original bone cavity was no longer filled with red granulation tissue, but consisted of several cystic cavities filled with clear fluid. Between these last curettages, he has been able to work as a barber, and his general physical condition is excellent.

Summary: The points of interest in this case are:

(1) A single, expansive tumor of the lower end of the tibia.
(2) Slow growth, over eight years' duration.
(3) Eight curettages for recurrence, which is always *in loco.*
(4) Absence of metastases.
(5) Excellent physical condition of patient.
(6) Typical gross appearance of tumor is changing from that of a cavity filled with red granulation tissue (chronic hemorrhagic osteomyelitis of Barrie) to that of bone cysts filled with clear fluid (chronic fibrocystic osteomyelitis of Barrie).
(7) Typical microscopical appearance of the so-called medullary giant-cell sarcoma or chronic hemorrhagic osteomyelitis of Barrie.

CASE II. *History:* T. K. Female; age twenty-five years; married; housewife. Family history: Negative. Past history:

Had measles in childhood; venereal diseases denied; has had four normal births, one miscarriage. In February, 1914, patient had a miscarriage; she lost considerable blood and has never been well since. She complained of weakness, dyspnœa, and palpitation on exertion. In August, 1914, she noticed a lump growing in the inner angle of right eye; this was the first tumor mass noticed. In October, 1914, she fell and broke right femur about six inches above the knee-joint. She was admitted to the City Hospital and the fracture united with good result. In February, 1915, she noticed a mass on the anterior surface of the left tibia, about its middle third, which grew for two months and attained the size of a hen's small egg; it then stopped growing. In May, 1915, she gave birth to a full term, healthy child. In June, 1915, she was admitted to the City Hospital, complaining of dyspnœa, weakness, cardiac palpitation and slight bone pains.

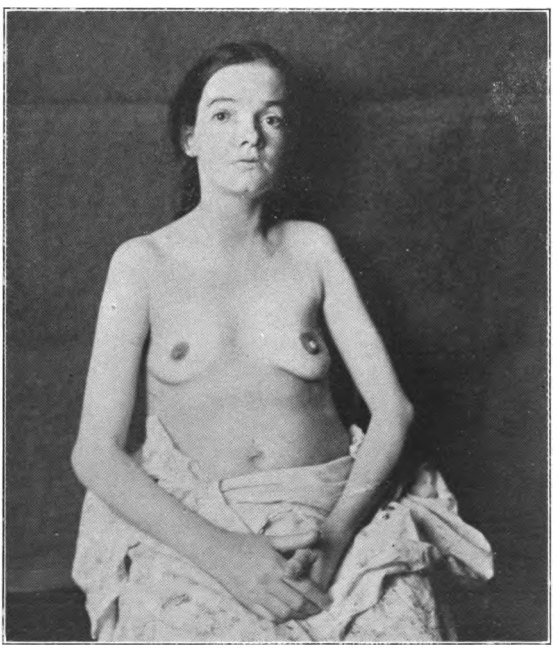

FIG. 1. Photograph of multiple bone tumor case, showing growth in right antrum.

Physical Examination: A well-developed female, fairly well nourished (Fig. 1). Nose, saddle shaped (due to trauma in childhood). Heart, apex in sixth interspace, outside nipple line; a loud mitral systolic murmur. Lungs, suspicious signs of early tuberculous involvement of left upper lobe. Rest of physical examination negative, except for the presence of palpable bone tumors. The right superior maxilla presented a hard tumor mass, which was infiltrating the inner wall and floor of the right orbital cavity. The left clavicle presented a hard mass the size of an English walnut at the sterno-clavicular joint. The right clavicle near its acromial end presented a hard tumor mass the size of an English walnut. The left tibia, on its anterior surface, and near its middle and upper third, presented a hard tumor the size of an English walnut.

Roentgenograms: Showed in addition to the palpable tumors, described above, expansive tumors in the following locations: In the seventh rib on the right side; in the right femur above the knee-joint (Fig. 2); in the right fibula on its upper third; and in the left fibula on its upper third (Fig. 3). Later roentgenograms showed a tumor developing in the right humerus just above the elbow (Fig. 4), and in the pelvis.

Laboratory Examinations: The following laboratory examinations were made:

Hæmoglobin .....75 to 85 per cent.
Erythrocytes .....4,020,000 (none abnormal)
Leucocytes .....5,200 to 9,600 (none abnormal)
Blood Wassermann negative, three times
Spinal fluid Wassermann, negative once, with normal cell count and globulin

Urine: Several 24-hour specimens were examined, especially for Bence-Jones albumose, with negative results. The urine always showed a trace of albumin, with a small number of hyaline and granular casts. Otherwise the urine was normal.

Clinical Diagnosis: From the above clinical facts a diagnosis of multiple myeloma, cardiac dilatation, and failing compensation was made.

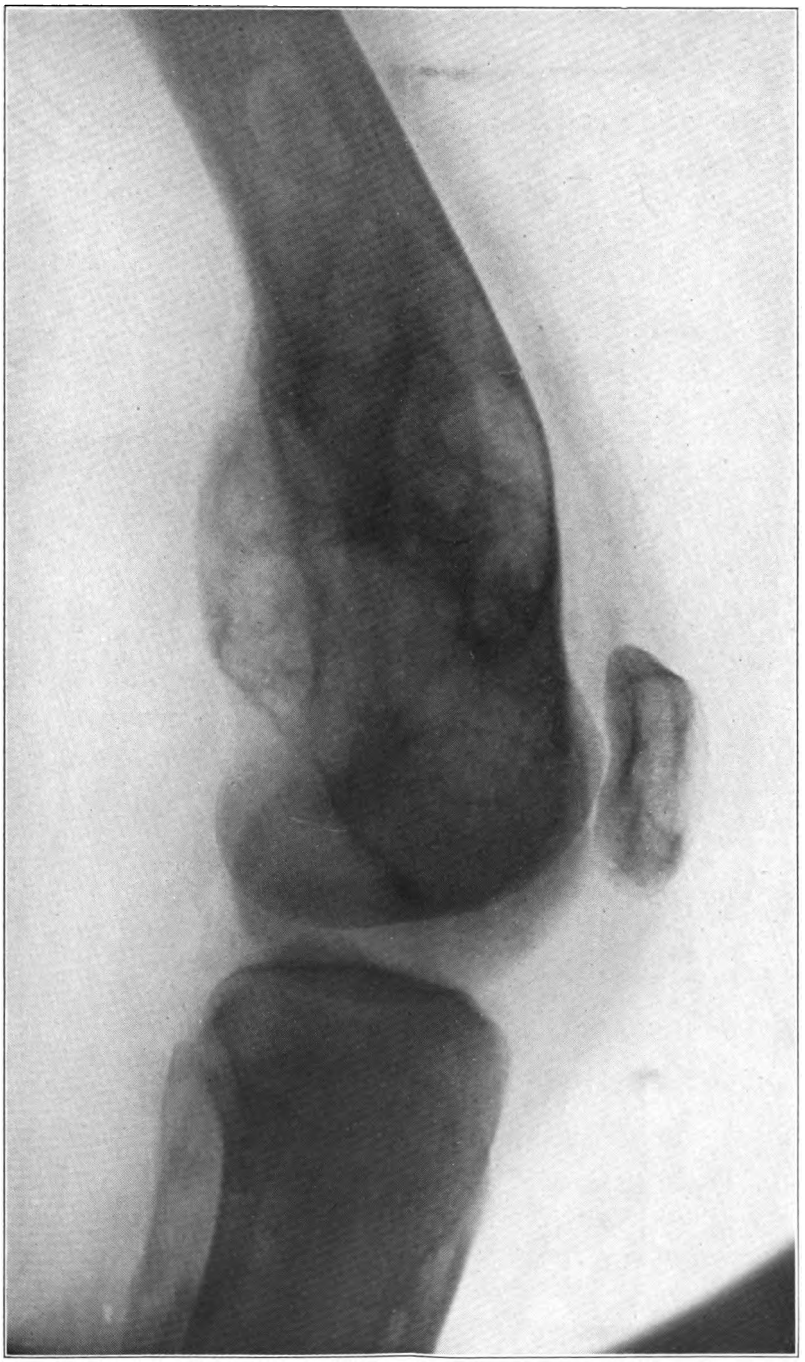

FIG. 2. Roentgenogram, showing expansive growth in lower end of right femur.

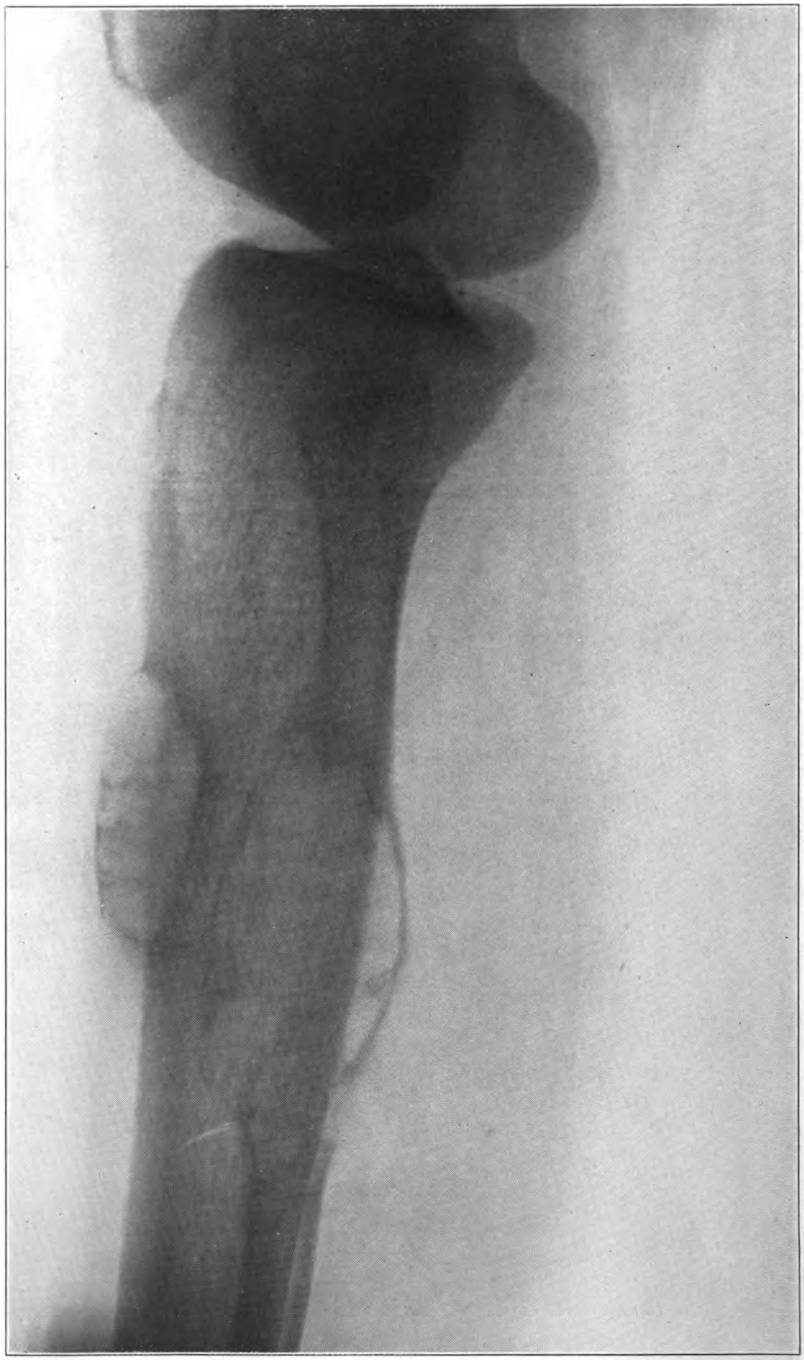

FIG. 3. Roentgenogram, showing expansive growths in left tibia and fibula.

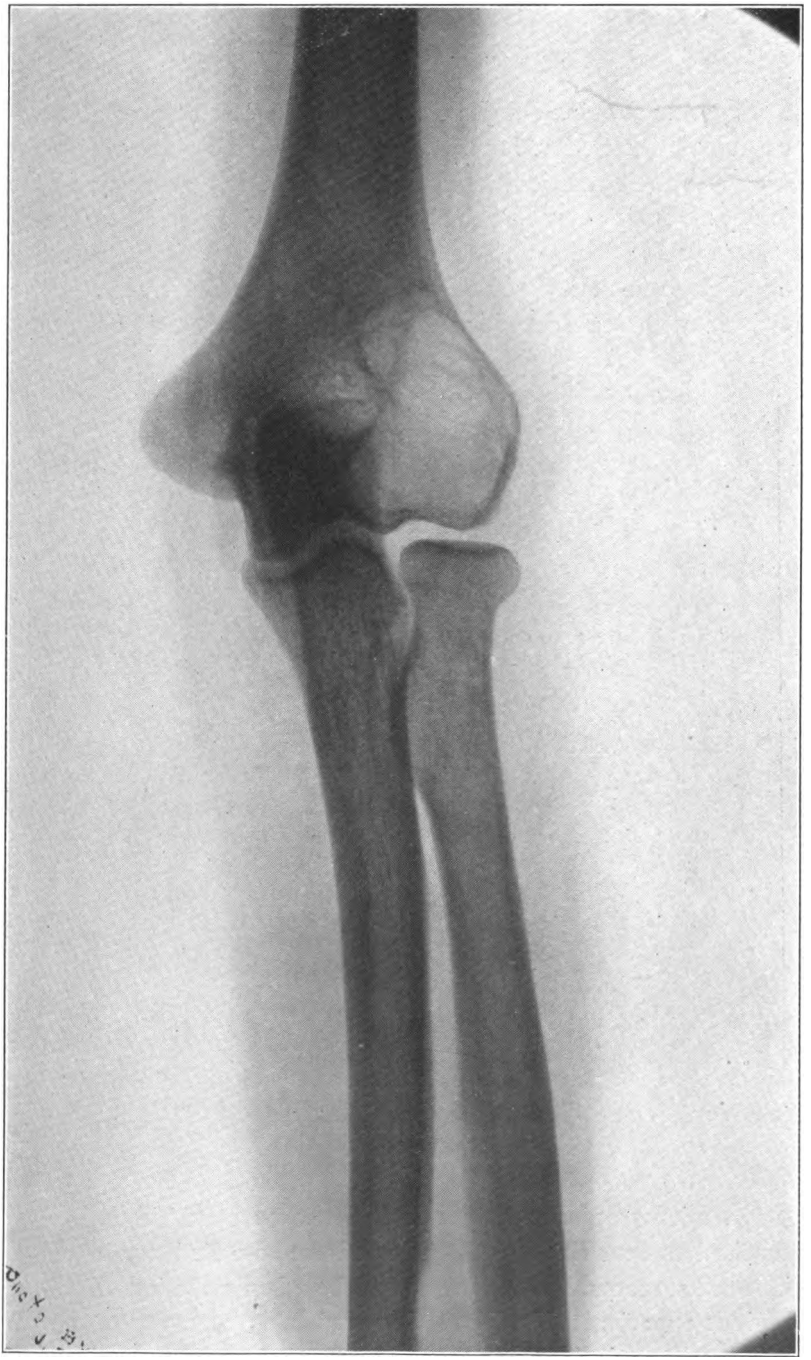

FIG. 4. Roentgenogram, showing expansive growth in lower end of right humerus.

Progress Notes: On June 28, 1915, in order to establish a positive diagnosis, Dr. Haussling curetted the growth on the left tibia. At the operation, he added the following notations to the history: "Incision revealed a small localized cavity, containing what appeared to be well-organized granulation tissue, reddish, and with considerable bleeding. Tissue curetted away, cavity swabbed with pure carbolic." Wound healed by first intention.

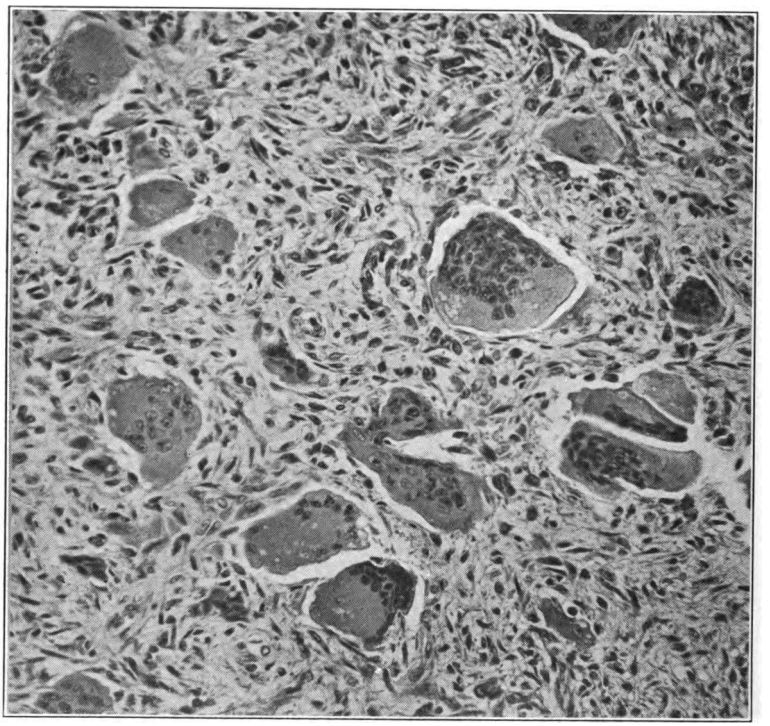

FIG. 5. Case II. One of the multiple tumors. Showing numerous giant-cells with fibroblastic stroma.

On microscopical examination of the curetted tissue, I was surprised to find the typical lesion of the so-called myelogenous giant-cell sarcoma. Believing this to be a benign lesion from our previous experience, Dr. Haussling decided to attempt to remove by the curette all the other tumor masses. On August 16, 1915,

a second operation was performed and tumor masses in the following locations were exposed and curetted: right fibula; left fibula; left clavicle; seventh rib and right superior maxilla. The following notation was made by Dr. Haussling at the operation: "The lesion in the superior maxilla seems to involve the entire antrum and to be encroaching on the right nasal cavity. All tumors are well localized, the line of demarcation of diseased and

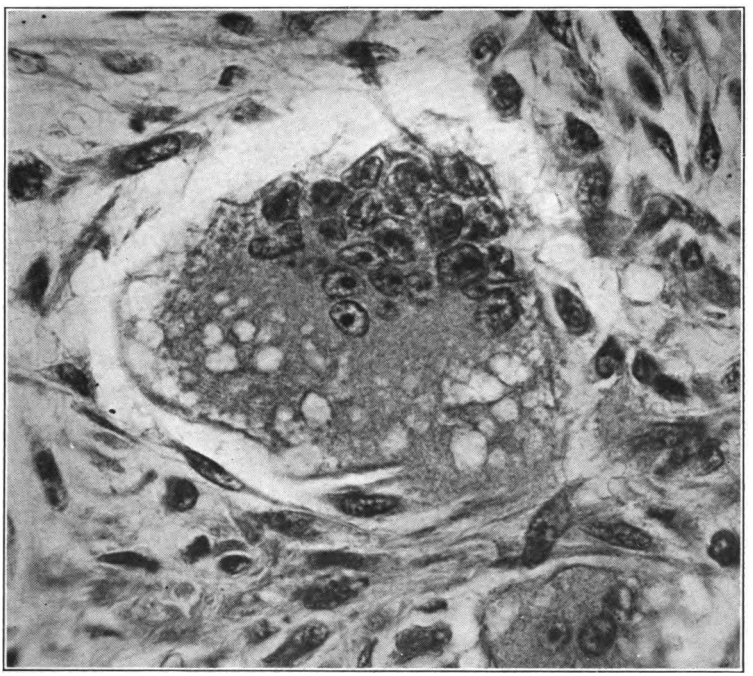

FIG. 6. Case II. High-power picture of typical giant-cell. Showing dark, abundant cytoplasm with numerous regular nuclei without mitotic figures.

healthy bone is quite sharp. The gross appearance is that of reddish, pale granulation tissue with considerable bleeding." All incisions healed by first intention. Microscopical examination of the various tumor tissue removed at the operation showed the typical picture of the so-called myelogenous giant-cell sarcoma (Figs. 5 and 6).

Subsequent Notes: The patient's physical condition has greatly improved; her cardiac condition has become fully compensated. The tumors curetted still show in roentgenograms, and new ones are slowly making their appearance.

Summary: The points of interest in this case are:

(1) Multiple, primary, expansive, slow growing bone tumors.
(2) Tumors too numerous and situation too varied to infer trauma as an etiological factor.
(3) Tumors are well localized and circumscribed.
(4) There is absence of infiltration of soft parts by any of the tumors, in fact, none of them have yet broken through their bony shell.
(5) There has been very little bone pain.
(6) There is absence of visceral or other metastases.
(7) There is absence of emaciation, in fact the physical condition improves.
(8) All incisions over tumors healed by first intention, a condition not often seen in malignant bone tumors.
(9) All tumors had a typical or characteristic macroscopical appearance, namely showing solid and cystic portions, the former predominating, and resembling reddish granulation tissue with free bleeding.
(10) All tumors presented the typical microscopical picture of the so-called medullary giant-cell sarcoma or the chronic hemorrhagic osteomyelitis of Barrie.

Discussion:

Dr. George Barrie: In cases of hæmorrhagic non-suppurating osteomyelitis, or the so-called giant-cell myelogenous sarcoma that I have seen, the roentgenograms were different and did not resemble those shown by Dr. Martland from the multiple bone tumor case. As regards Mallory's views, I do not think the instances he has reported should be regarded as typical.

Dr. Coley: In any discussion pertaining to the question: whether myeloid tumors are benign or malignant, one must first determine what is meant by the term "myeloid sarcoma." One surgeon will call the small and sharply defined non-infiltrating tumors of the bones "malignant or round-celled sarcoma," while most of these are benign; and another includes in the term "myeloid sarcoma" all endosteal tumors, many of which are of extreme

malignancy. One of the most important discussions of Tumors of the Long Bones was held at the Royal Society of Medicine in London (November, 1912). In the course of the discussion, Sir Frederick Eve stated that it was an error to consider all myeloid tumors as benign. Mr. Gilbert Scott, of London, stated that while the majority were benign, some of them were not only malignant, but showed a very marked degree of malignancy. Mr. R. C. Maybury cited two cases of myeloid sarcoma, observed at St. Thomas' Hospital, both of which were followed by general metastases which proved fatal.

The second case reported by Dr. Martland this evening had none of the clinical features of ordinary myeloid sarcoma of the long bones, nor did the *x*-ray picture point to such a condition. Dr. Coley stated that he believed the nearest approach to such a case as the one just observed was a case of Dr. Gibney's, in which slow-growing tumors developed in one long bone after another (usually followed by spontaneous fracture) until a large number of the bones were involved, finally causing death. The *x*-ray picture of these lesions is shown in Dr. Coley's recent paper on "Some Problems in the Early Diagnosis and Treatment of Sarcoma of the Long Bones" (*Annals of Surgery*, November, 1914).

Dr. Coley stated that he did not agree with Dr. Bloodgood and some others, who regard all cases of myeloid sarcoma of the long bones as benign. In his paper, referred to above, may be found a microscopical photograph of a tumor which occurred in the upper part of the humerus, in a boy ten years old. The growth attained its largest size three weeks after the injury. The clinical symptoms in this case pointed so clearly to a highly malignant sarcoma that Dr. Coley decided to perform immediately an amputation at the shoulder-joint, without waiting for a microscopical section. This he did, and later submitted a specimen of the tumor to Dr. Ewing, who pronounced it a giant-celled sarcoma of the epulis type showing only a moderate degree of malignancy. Dr. Ewing believed that Dr. Coley had made a mistake in amputating in a case that he thought could have been cured simply by curetting. In spite of the very radical operation, which was followed by a short course of toxin treatment, extensive metastases developed in the lung and the boy died within a year.[1]

Dr. Coley showed *x*-ray photographs of two cases of central sarcoma, recently observed at the Hospital for Ruptured and Crippled, one occurring in the humerus and the other in the tibia; both were classified by the pathologist as giant-celled sarcoma. Nevertheless, the clinical course of the disease proved it to be of a high degree of malignancy. In the first case there was extensive invasion of the knee-joint by a tumor of eight months' duration, and the whole lower end of the femur was destroyed. In the second case, the whole upper end of the femur was destroyed and extensive involvement of the fibula had taken place within seven months.

[1] It is only fair to state that on later examination of the specimen by Dr. Ewing he inclined to the belief that the tumor belonged to the type of bone aneurism, of a very high degree of malignancy, and that his original diagnosis was undoubtedly erroneous.

DR. LAMBERT: I was very much interested in the second case of Dr. Martland. I would like to ask if any other such cases have been reported. Regarding Dr. Coley's remarks, he tells us that he has seen examples of a typical giant-cell myeloid sarcoma of a highly malignant character. I wish he had brought sections from those tumors. I am inclined to think that he has confused the giant-cell myeloid sarcoma with the mixed sarcoma of bone, in which multinucleated cells are found. The latter tumor is, however, quite different from the former, both clinically and pathologically. The former is characterized not only by the presence of numerous large giant cells, but by an abundant connective tissue.

To regard the giant cells in myeloid sarcoma as accidental foreign-body giant cells, as Mallory does, appears to me to be without basis. Their formation is too uniform and constant to admit such an interpretation. Furthermore, foreign particles are not found in these cells.

DR. MARTLAND: In the multiple case the clinical appearance is like multiple myeloma. Histologically we find it resembling the single tumor case, therefore I was led to believe that these multiple growths were of the same nature and that they were benign in character. I do not believe that the tumors in this case will ever metastasize into the soft parts. The case will be carefully followed and will no doubt come to autopsy, and nothing will ever be satisfactorily determined until then. I think the antrum tumor will grow so large that it will invade the ethmoid cells and cause a meningitis, but I do not think she will ever die of metastases. I can find no evidence in literature of any case of multiple tumors of slow growth which have the same histological picture. As far as hypernephroma is concerned, we do not think it necessary to consider that in this case.

EQUILIBRIUM IN THE COMBINATION AND THE DISSOCIATION OF PRECIPITATES

RICHARD WEIL, M.D.

It has been shown by Linossier and Lemoine that if horse serum or other similar antigen be mixed with its specific precipitating anti-serum, the resulting precipitate never exhausts completely either of these two factors. Both of them can always be shown to be present in the supernatant fluid. This has been confirmed by Eisenberg and others. Moreover, the serum of immunized animals has been shown under certain circumstances to contain both precipitin and precipitinogen. By the original observers this was interpreted as an instance of the laws of mass

action. Zinsser and Young interpreted it on the analogy of the protective action of a third colloid on two mutually precipitating colloids. Von Dungern attributed the observation to the presence of a multiplicity of antigens in the horse serum, or similar antigenic substance, with a corresponding mutiplicity of antibodies. The whole phenomenon, upon this basis, is reducible to a fallacy of technique. This theory was not supported by experiment and has not found further acceptance.

In order to test this theory a chemically pure antigen was prepared, namely crystalline egg albumen. When this is mixed with its anti-serum a precipitate results. The supernatant fluid can always be shown to contain either one of the two factors, egg albumen or antibody, but never both at the same time. This is true no matter how the proportions may be varied. With raw egg albumen and its anti-serum, on the other hand, the relations are the same as described by Eisenberg. The conclusion is drawn that Von Dungern's theory is correct. Under proper experimental conditions the precipitation reaction goes on to the complete exhaustion of either factor. "Equilibrium does not exist."

By means of absorption experiments it was shown that raw egg albumen contains not only the substance isolated as crystalline egg albumen, but also other antigens. Likewise, the anti-serum to raw egg albumen was shown to contain a mutiplicity of antibodies. This confirms the previous conclusion.

In view of the fact that equilibrium in precipitation reactions does not exist, it is unnecessary to consider the explanations offered therefor. It is of interest to note, however, that the presence of either small or large amounts of serum, such as rabbit serum or guinea-pig serum, added to the above mixtures, does not in the slightest interfere with the completeness of the reaction. There appears, therefore, to be no analogy in this instance with the protective action of a third colloid.

Dissociation of precipitates has recently been studied by Chickering in connection with an extract of pneumococcus and its

anti-serum. He used salt solution, or a one per cent. solution of sodium carbonate. He found that the extract contained no antigen, but did contain protective antibody and agglutinin. In my own experiments in dissociating the precipitate produced by horse serum, or egg albumen, and its appropriate anti-serum, different results were obtained. If the precipitate was treated with salt solution or sodium carbonate, antigen could always be demonstrated in the extract. It contained no precipitin, but did contain antibodies conferring passive sensitization. If the extraction was performed with trypsin or with rabbit's leucocytes, both antigen and precipitin could be demonstrated in the fluid. These reactions, like those previously described, have no analogy either in mass action or in colloidal chemistry.

Discussion:

DR. FIELD: I would like to ask Dr. Weil how far digestion was carried with the leucocytes and trypsin. In Osborne and Mendel's work, when they carried digestion to completion there was loss of toxicity. This is used in testing the activity of proteolytic enzymes. In regard to the sodium carbonate and sodium chloride it might be due to precipitation.

DR. ZINSSER: In a matter of this kind time is needed for the discussion. I do not think it is logical, on the basis of these observations, to minimize the analogy between colloidal chemistry and serum reactions. In the precipitin reaction we have the influence of salts which is a striking analogy. We have the inhibition zones and the influence of quantitative relations on the reaction. We are dealing with obscure phenomena and must call analogy to our help and we have a right to reason from it, and the analogy to colloidal chemistry is too valuable to be disregarded. Five or six years ago Dr. Young and I were working on this problem. We did not consider the explanation of Von Dungern as likely. In our work we found that when we allowed the serum to stand it would precipitate spontaneously. The antibodies in the supernatant fluid would correspondingly diminish. This we thought was a reasonable argument that the antibody antigen complex came together by slow union. This, too, is analogous to colloidal suspensions where slow precipitation occurs even in the presence of a protective colloid. The mass action idea we did not consider correct because the sera themselves gave no complement fixation. This test is not absolute proof but it is the only indicator available. If the mass action idea was correct, then the serum itself should have contained antigen-antibody united as well as dissociated, and this complex, as far as we have any reason to argue from experience, should have fixed complement. I think that the precipitation phenomena of serum are too difficult at present to throw out peremptorily any help we get from colloidal analogy. So far as separation of the anaphylactic antibody

from the precipitins goes, I may say that I have been one of those who for a number of years have maintained, both in experiment and in reasoning from the work of others, that there is only one antibody of which precipitation, agglutination, and other antibody reactions are different manifestations, depending upon the conditions under which the reactions are carried out and the nature of the antigen.

DR. FIELD: In regard to the question of colloids and mass action, I used to use the term colloid chemistry, but I am sure we have got to be on our guard in making use of these names. I think the types of reactions between ions of extremely small size and molecules of larger size, and passing to molecules of organic compounds and then to colloidal gold and finally to clay and carbon, differ only slightly from each other.

DR. ZINSSER: I think that what Dr. Field says is true, and that no one has thought of disputing the perfectly self-evident statements he has made. That we are dealing with larger particles in one case and with smaller ones in the other, and, in the case of the larger particles, often with substances that are not chemically analyzable, is perfectly true, but it is also true that the methods of study of these two different kinds of substances are necessarily different, and since we believe that antigen-antibody reactions are of the latter nature, we apply these latter methods to their study.

DR. WEIL: The remark has just been made that the argument from colloidal reactions is really only a "cloud to cover our ignorance," and I think this remark truly conveys the gist of the whole matter. Instead of solving the problems of immunology we have been using the analogies of colloidal chemistry to veil our ignorance of the situation. I believe that the dangers and fallacies of such a course are evident from the results of the experiments which I have described this evening. The actual results of the immunological experiment do not in the least correspond to the analogy which had been drawn from the reactions of colloidal chemistry. This danger was long ago emphasized by Buxton, and even by Bordet, the arch-exponent of the colloidal interpretation. As regards the particular questions brought up, the problem of auto-precipitation would require too long a time for discussion here. I may say, however, that I do not agree with Dr. Zinsser's interpretation of this phenomenon. A full discussion of that phase will be presented in a publication of mine which will soon appear. There is another point in my paper to which Dr. Zinsser took exception, namely, the question of separation of the precipitin from the anaphylactic antibody. He feels that they are the same substance. I entirely agree upon that point. The two functions, however, namely, precipitation and passive sensitization, may be differentiated and separated. I have found that it is possible by heating precipitin to 72 degrees to deprive it completely of its precipitating effect, while the sensitizing value is retained almost unimpaired. In the terminology of Ehrlich the so-called ergophore group of the antibody, which is essential to precipitation, may be sacrificed, while leaving intact the so-called haptophore group, which alone is necessary for anaphylaxis. This observation, which is, I believe, of great importance for the understanding of anaphylaxis, has not been hitherto reported. It answers Dr. Zinsser's objection satisfactorily.

GROUPING OF MENINGOCOCCUS STRAINS BY MEANS OF COMPLEMENT FIXATION

MIRIAM P. OLMSTEAD

A study of literature on the meningococcus shows that while the complement fixation method has been used extensively in titrating serum and to a slight extent for diagnosis, except for work with the para-meningococcus practically no attempt has been made to use it in grouping strains of meningococci.

The work I am to report this evening has been done in collaboration with Dr. Phoebe DuBois, Dr. Josephine Neal and Miss Rose Schweitzer.

To obtain immune serum rabbits were inoculated by ten intravenous injections of live culture, administered every third day. The dose was increased from one fourth to a whole slant culture, washed off with normal saline. The cultures for inoculation were twenty-four hour growths in neutral veal agar.

Antigens were prepared according to the method suggested by Schwartz and McNeil for gonococcus antigen.

The total volume of the test was 0.5 c.c., one tenth that of the classical Wassermann. The anti-sheep system was used, cells in a five per cent. suspension, from one to two units of amboceptor, and guinea-pig serum for complement in a ten per cent. dilution. The system was carefully standardized each day by an amboceptor titration. Sensitized cells were used and the readings of antigen and antibody content titrations were made the next day, after the cells had settled.

The sera were freshly inactivated each day by heating for one half hour at 56° C.

Antigen and serum titrations were performed according to the technique described in Park and Williams' *Pathogenic Microorganisms,* 1914, pp. 184–187. The anticomplementary dose of antigen has been determined by testing decreasing amounts of antigen (0.3, 0.2, 0.1, 0.05 c.c.) in various dilutions. The antigen unit, by which is meant the smallest amount of antigen that gives complete inhibition of hemolysis with about

two units of homologous immune serum, has been obtained by testing decreasing amounts of antigen (0.25, 0.2, 0.15, 0.1, 0.05, 0.025 c.c.), with 0.01 c.c. of serum. The anticomplementary property of the serum has been tested in 0.04 c.c. and 0.02 c.c. of undiluted serum. The antibody unit, by which is meant the smallest amount of serum that gives complete inhibition of hemolysis with about two units of homologous antigen, has been obtained by testing decreasing amounts of serum (0.02, 0.01, and of a ten per cent. dilution 0.09, 0.08, 0.07, 0.06, 0.05, 0.04, 0.03, 0.02, 0.01 c.c.), with about 0.1 c.c. of antigen.

The work on the differentiation of meningococcus strains was begun with neither antigen nor serum standardized. A polyvalent antigen of all the strains was made and standardized with 0.01 c.c. of serum from a horse immunized against all the strains. The polyvalent horse serum was then titrated with one and one half units of the polyvalent antigen and used in standardizing all the monovalent antigens. Each monovalent antigen was titrated in several dilutions to obtain the antigen unit. From one and one half to two units of the monovalent antigen thus standardized were used in standardizing its homologous immune serum. Any antigen so poor that double this amount was anticomplementary was discarded and not used for serum titrations. Serum was also titrated in a sufficient number of dilutions (1 in 10, and 1 in 100) to determine the antibody unit. From one and one half to two units of serum (diluted so that 0.01 c.c. contained that amount) were used in making the antigen cross-titrations. The specificity of the antigens was tested by titrating against a known positive gonococcus serum with practically negative results.

Rabbits were immunized against forty strains of meningococcus, but the cross-fixation work was carried out completely with only twenty-nine of these strains. Each antigen and each serum were titrated against all the strains in several dilutions until the smallest amount of both antigen and serum that gave complete inhibition of hemolysis was determined.

The results of antigen titrations are summarized in the table.

Of the twenty-nine strains of meningococcus tested, fourteen

fell into one group, eight into another, two cross-fixed with each other only by both antigen and serum titrations, two did not fix with any other strain and three acted irregularly. Strains 1, 3, 4, 7, 8, 19, 20, 21, 22, 23, 24, 26, 28, and 34 cross-fixed with

TABLE I

Antigens of Twenty-two Strains Titrated Against Sera of Various Strains

Antigen Strains	Immune Sera of Group I									Immune Sera of Group II						Immune Sera of Irregular Strains			Immune Sera of Odd Strains			
	1	3	4	7	20	22	23	24	28	10	11	13	14	16	18	2	12	27	6	29	15	17
1	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−
3	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−
4	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−
7	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−
8	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−
19	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−
20	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−
21	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−
23	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−
26	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−
28		+	+	+	+	+	+	+	+	−	−	−	−	−	−		−	−	−	−	−	−
34		+	+	+	+	+	+	+	+	−	−	−	−	−	−		−	−	−	−	−	−
9	−	+	−	−	−	−	−	−	+	+	+	+	+	+	−	−	−	±	−	−	−	−
10	−	+	−	−	−	−	±	−	+	+	+	+	+	+	+	−	−	±	−	−	±	−
16	−	+	−	−	−	−	−	−	±	+	+	+	+	+	−	−	−	−		−	−	−
18	−	−	−	−	−	−	−	−	−	+	+	+	+	+	+	−	−	+	−	−	−	−
32	−	−	−	−	−	−	−	−	−	+	+	+	+	+	+	−	−	−	−	−	−	−
2	+	+	+	+	−	+	+	+	+	−	−	−	−	−	−	+	−	−	−	−	−	−
27		+	+	+	−	+	−	−	+	−	−	−	−	−	−		−	+	−	−	−	−
6	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−
29	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−
15	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	+

+ Denotes complete inhibition of hemolysis in as small an amount of antigen with heterologous as with homologous serum.

± Denotes complete inhibition of hemolysis, but not in so small an amount of antigen with heterologous as with homologous serum.

— Denotes incomplete or no inhibition of hemolysis.

each other, forming Group I (Tables I and II). Strains 9, 10, 11, 13, 14, 16, 18, and 32 cross-fixed with each other, forming Group II (Tables I and II). Antigens of Group I did not fix

any sera of Group II, but antigens 9, 10, and 16 of Group II fixed some sera of Group I. Antigen titrations only of strains 21 and 26 were made against other single strains, as the rabbit

TABLE II

Immune Sera of Twenty-four Strains Titrated Against Various Antigens.

Serum Strains	Antigens of Group I											Antigens of Group II						Antigens of Irregular Strains			Antigens of Odd Strains		
	1	3	4	7	8	19	20	22	23	24	28	9	10	13	14	16	18	2	12	27	6	29	15
1	+	+		+	+	±	±	+	±	±	±	−	−	−	−		±	−	±	−	−	−	−
3	+	+	+	+	±	±	+	+	+	+	+	+	+	+	+		±	+	±	+	−	−	−
4	+	+	+	+	±	−	+	+				−	−	−	−	−	−	−	−	−	−	−	−
7	+	+	+	+	−	−	+	+	+	+		−	−		−		−	−	−	−	−	−	−
8	+	±	+		+		+	+				−	±	−	−		−	±	±	−	−		−
19	+	+	+	+	+		+					+	+		−		+	±	−		−	−	−
20		+	+	+	+	−	+	+				−	−	−	−	−	−	±	−		−		
22	+	+	+	+	±	±		+				±	±	±	±		±	±	±		−		
23	+	+				+	+					±	±	±			±				−	−	
24	+	+		+		+	+					+	+				±		+	+	−	−	
28	+	+		±				+				+	+		−		−	+			−	−	−
9	±	±	±	±	±			±	±			+	+	+	+			±	±		−		
10	±	+		±	±			−				+	+	+	+	+	+	±	±	−	±	−	
13	±	±	±	±	±			±				+	+	+				±	±		±		
14	±	±	±	±	±		+	±				+	+	+	+	+	+	±	±	+		−	−
16	±	±	±	−	−	−		±				+	+			+	+	−	−		−		
18	+	+		+	+		−					+	+			+	+	−	+		−		−
2	−	−	−		−	−		−				−	−		−	−	−	+	−	−	−	−	−
12	±	±	±		±							±	±		−			±	+		−	−	±
27	±	−	±	−			±					±	±			±	±	−		+	−		−
6	±	−	−	−	−	−	−	−	−	−	−	−	−	−				−	−	−	+	−	±
29	−	−	−	−			−					−	−		−		−	−	−		−	+	−
15	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−		−	−	−	−	−	−	+
17	±	±	±	−	−	−	−	−	±	−	−	−	−	−	−		−	−	−	−	−	−	+

+ Denotes complete inhibition of hemolysis, in approximately the same amount of serum with homologous and heterologous strains.

± Denotes complete inhibition of hemolysis, but not in so small amount of serum with heterologous as with homologous strains.

— Denotes incomplete or no inhibition of hemolysis.

sera of these strains lost their antibody content before serum titrations could be performed. These strains were not included

in an antigen made of six strains (3, 21, 10, 18, 2, and 12). The sera of these strains (21 and 26), however, gave fixation with this polyvalent antigen and the antigens of these strains fixed all the sera of Group I, hence, we concluded that these strains belonged to Group I. Antigens of strains 6 and 29 gave fixation with their homologous sera only and sera 6 and 29 gave fixation with their homologous antigens only. Antigens and sera of strains 15 and 17 cross-fixed with each other. Strains 2, 12, and 27 acted irregularly. In the antigen titrations of these strains cross-fixation occurred with the sera of Group I, but the immune sera of strains 2, 12, and 27 fixed complement with their homologous antigens only.

Sera of twelve strains (1, 3, 4, 7, 8, 19, 20, 21, 23, 24, 26, and 28) of Group I, seven strains (9, 10, 11, 13, 14, 16, and 18) of Group II, the irregular strains 2, 12, and 27, the odd strains 6, 29, 15, and 17, and nine unidentified strains (31, 32, 33, 34, 36, 37, 38, 39, and 40), were titrated with a polyvalent antigen consisting of strains 3 and 21 of Group I, 10 and 18 of Group II and the irregular strains 2 and 12. The relationship of strains 6, 15, 17, 27, and 29 had not been determined at the time this antigen was made or they would have been included. These strains only gave no fixation with the antigen, but our later work demonstrated that they were not related to any of the strains included in the antigen.

As stated above, the monovalent antigens were standardized with the polyvalent immune horse serum for the serum cross-titrations, which were made before the antigen cross-titrations. We found after we had done the antigen cross-titrations, that the antigens gave a much longer range of fixation with their homologous immune rabbit serum than with the polyvalent horse serum. It seems, therefore, that so much antigen was used in the serum cross-titrations that a group reaction occurred. This may explain why a more distinct differentiation of strains was obtained by means of antigen titrations than by means of antibody content titrations.

Complement fixation is such a delicate method of differen-

tiating strains of an organism that it is difficult to obtain absolutely consistent results. The age and antibody content of a serum, the range of the antigen, the strength of the complement, the interval between the completion of the test and the reading of the same, the temperature of the ice-box, and the frequency of standardization of sera and antigens are factors that greatly influence the test.

A study of the history of the strains proves that the clinical history of the case has nothing to do with the grouping.

Strains causing severe reactions in rabbits—it being necessary to try several rabbits before one could be found that could be immunized—were:

1, 2, 7, 16, 18, and 24,—
1, 7, and 24 are in Group I,
16, and 18 are in Group II, and
2 in irregular Group.

Thus it appears that no relation exists between virulence and grouping. Neither is there any relation between length of time strains had been isolated and grouping. Group I contained the oldest and the newest strains.

The subject of the para-meningococcus has received considerable attention in France for the last few years, due to the work of Dopter, Menetrier and others. This work has been done along both clinical and laboratory lines. Patients suffering from meningitis that did not respond to the ordinary anti-meningitis serum improved under the use of a para-meningitis serum prepared by Dopter in 1912. Dopter in 1911 in studying the so-called para-meningococcus, found that he could not differentiate these strains from normal meningococcus by using them as antigens with polyvalent horse serum, but that they could be differentiated by the serum of patients, as the serum of patients suffering from meningococcic meningitis did not fix a para-meningococcic antigen, and the sera of patients suffering from para-meningococcic meningitis did not fix with a meningococcic antigen.

Wollstein in 1914 published a very careful study of the para-meningococcus in which she arrived at similar conclusions using the sera of rabbits immunized with single strains of meningococcus and para-meningococcus instead of the sera of patients. She concluded: "The para-meningococci of Dopter are culturally indistinguishable from true or normal meningococci, but serologically they exhibit differences as regards agglutination, opsonization, and complement deviation."

By the agglutination method strains 7 and 42 are classed by her as para-like strains. She did not give the results of complement fixation with these strains. In our work it was found by complement fixation that strain 7 fell in Group I and strain 42 in the irregular group allied to Group I. As transplants of two Dopter para-meningococcus strains, P. L. and P. M., were kindly given us by Dr. Wollstein, we were enabled to test them against our strains. We found antigens of P. L. to react with homologous serum only, and antigens of P. M. to react with the sera of Group II.

Now if the para-meningococcus is to be separated from the normal meningococcus by serological reactions and if agglutination and complement fixation yield different results with the same strains, the question is indeed a perplexing one. With the method used by us, the results yielded by the complement fixation test have been fairly uniform and specific. By this method the strains have fallen into various groups, containing a varying number of strains. Shall we call all the strains except those in Group I para strains, or shall we call them simply groups of normal meningococci? The question is purely academic, yet it is of some importance since the employment of the term "para" differentiates the strains more than seems justifiable. It is perhaps better, therefore, to classify them as belonging to a group co-ordinate with other meningococcus groups.

Wollstein further concludes: "Because of the variations and irregularities of serum reaction existing among otherwise normal strains of meningococci it does not seem either possible or desirable to separate the para-meningococci into a strictly definite class.

It appears desirable to consider them as constituting a special strain among meningococci not, however, wholly consistent in itself." This conclusion we would heartily endorse.

CONCLUSIONS

By means of complement fixation the meningococcus may be clearly differentiated from allied organisms. A differentiation of individual meningococcus strains is possible by the use of refined technique, but the relationship of strains is so close that it is difficult to obtain absolutely clear cut and consistent results. Of the twenty-nine strains studied by us, fourteen seem to form one group and eight a second group. Three seem to be closely related to the first group but have acted so irregularly that they cannot be classed with it, two have shown a relationship with each other only and two have shown a relationship to no other strain.

Discussion:

DR. ZINSSER: The difficulty of separating and classifying the various strains of meningococci is well known. This is the first serious attempt to clearly separate the different strains by complement fixation tests.

THE PRACTICAL SIGNIFICANCE OF THE OXIDASE REACTION AS APPLIED TO BLOOD CELLS

F. A. EVANS, M.D.

For some time it has been known that the cells of myeloid origin contain granules of oxidase ferment and those of lymphoid origin do not, and an appreciation of the practical significance of this difference has led to many attempts to perfect a convenient method of demonstrating the presence or absence of the ferment in any given cell. As early as 1887, Vitali made the observation that the guaiac test for blood was of no value in the presence of pus, but Brandenburg[1] in 1900, was the first to notice that blood of leukemic patients frequently gave a positive guaiac reaction

without the presence of any oxygen bearer as peroxide or ozonized turpentine. Meyer[2] in 1903, demonstrated this phenomenon in the blood of myeloid leukemia but failed to obtain the reaction in that of lymphoid leukemia and called attention to the interest that attached to this reaction in view of Ehrlich's recently propounded dualistic theory of blood cell origin. This guaiac test was too crude to be of any practical value however, so Winkler[3] in 1907, applied the indophenol-blue synthesis of Ehrlich[4] (alphanaphthol + dimethylparaphenylendiamin with two atoms of oxygen form indophenol-blue) to smears of pus and tissue sections and with it found these granules of oxidase ferment as blue-black dots in the protoplasm of myeloid but not of lymphoid cells. He at this time predicted the usefulness of this reaction in the study of the origin of white blood cells, and it is the practical value of this test that we have under consideration this evening.

Schultze[5] submitted sections of many body tissues to this reaction after formalin fixation and found the granules only in the tear and thyroid glands and in cells of myeloid origin, and used the test in the differential diagnosis of the leukemias. Gierke,[6] using fresh tissue, found these granules in many body cells but after formalin fixation as used by Schultze obtained similar results. He suggested the hypothesis that this reaction on fresh tissue depended on the circulating respiratory oxygenase destroyed or inactivated by formalin fixation whereas the more stable oxidase of the myeloid cell endures. This work of both Schultze and Gierke has been repeatedly confirmed by other observers.[7] Gierke also refuted Dietrich's[8] statement that the oxidation is brought about by the tissue metabolism and the preformed indophenol-blue taken up by the fat droplets, by showing that no granules appear after killing the ferments and adding the already oxidized solutions, and that granules still give the reaction after killing the cell life by chloroform but preserving the oxidases. This indophenol-blue reaction appears, therefore, to be a reliable method, but although much superior to the guaiac test, because of technical difficulties is not all that is to be desired.

For fixation, only methods are available that do not injure ferments and as shown by Gierke,[6] formalin must be used in some form. Similarly counterstaining is difficult for only aqueous solutions used without a mordant are permissible, and any method of differentiating destroys the reaction in some cells. Furthermore, inasmuch as this indophenol-blue deposited in the granules of oxidase ferment is soluble in alcohol, ether, chloroform, aceton, xylol, and creosote, clearing of tissue sections is impossible and the mounting media are almost limited to materials soluble in water. Also, the preparation is not permanent, for the oxidase reaction only endures in its original intensity for about an hour, and the counterstain tends to be dissolved out by the aqueous mounting medium.

In spite of these difficulties, methods of application have been devised that are of practical value for tissue sections and especially for smears of blood and body fluids. For tissues, paraffin sections may be used if fixed primarily in formalin or preferably Bonn solution (Carlsbad salts 5, formalin 12.5, water 100 parts) as suggested by Fursenko,[9] for the materials used in preparation presumably do not injure the ferments. Frozen sections freshly cut give reliable results more constantly and are to be preferred. The section is immersed for about two minutes in a mixture in equal parts of the reagents freshly made up:

(1) 1 per cent. alpha-naphthol in 1 per cent. KOH.

(2) 1 per cent. aqueous dimethylparaphenylendiamin.

These solutions should be mixed just before using for if they are allowed to stand together for any length of time they combine with the oxygen of the air with the formation of indophenol-blue and confusing artefactions are likely to occur if granules of this preformed indophenol-blue are deposited on the section. The tissue removed from this mixture is washed, counterstained for a few moments in 5 per cent. pyronin or saturated aqueous safranin, washed again, and mounted in glycerin or a sugar mixture. Such a preparation shows the nuclei stained a deep orange-pink and the myeloid cells standing out by reason of the blue granules in their protoplasm. However, owing to the im-

possibility of clearing the section satisfactorily and the somewhat indefinite counterstaining, reliable identification of the individual cell as polymorphonuclear, myelocyte, or other, is frequently difficult. For this purpose parallel sections must be stained with hematoxylin and eosin and corresponding fields compared; or the field showing oxidase-containing cells may be drawn with a camera lucida, and the same section then stained with hematoxylin and eosin. If a frozen section has been used, after removing the cover slip and washing, the section is best dried and fixed to the slide with thin celloidin solution. Without these auxiliary procedures, the reaction is of value in demonstrating mild grades of infection in cellular tissues as the appendix and tonsil, and in demonstrating myeloid infiltration of organs in leukemia; and with them may be used to advantage in studying any obscure body cell. Many modifications of the indophenol-blue reaction have been suggested by Loele,[10] Schultze,[11] Kreibich,[12] and others,[13] whereby permanent preparations that may be cleared and counterstained may be had, but in all of these so many other factors are to be considered that their specificity for the myeloid cells may be seriously questioned. These modifications, although of great interest in the field of vital staining,[14] do not displace the original indophenol-blue reaction.

For smears of blood and other body fluids a satisfactory and more direct technique is available. Fixation is the most important step and for this, exposure to formalin vapor in a closed jar is the only satisfactory method. Very weak solutions of formalin (4 per cent.) for long periods (3–4 hours), depending on the age and thickness of the smear, are better than using stronger solutions for shorter periods, for with the weaker solutions the annoying tendency of the fixed smear film to wrinkle up when the indophenol-blue solutions are added, is not so marked. For smears, in contrast to tissue sections, the staining is best done first and for this the same solutions, 5 per cent. pyronin or saturated safranin, have proved the most satisfactory. Either of these allowed to remain on the smear a short time and then thoroughly washed off brings out the nuclei a deep orange-

pink that readily admits of the identification of the cell and leaves the other elements unstained. Such a preparation is then examined until a field containing cells in question as regards their oxidase content is found, and the slide clamped down. One drop of each of the solutions of the indophenol-blue reaction made up as outlined above is then added directly to the smear and the progress of the reaction watched with the low power objective in the cells being investigated till it has reached its maximum intensity in about two minutes. The smear may then be blotted carefully and the preparation examined with the high dry objective. It is essential that the cells in question be located before putting on the solutions of the indophenol-blue reaction and that the progress of the reaction be watched, for the stain is rapidly dissolved out of the nuclei by the alkaline solutions used and shortly after adding, especially if some wrinkling of the film as frequently occurs is present, identification of the cells becomes impossible. But if these details are observed a useful preparation results which shows oxidase granules in polymorphonuclears, myelocytes, myeloblasts, transitionals, and probably some large mononuclears, but in no lymphocyte. As in tissue sections the reaction is of value in the study of cells of uncertain identity and is especially useful in the differential diagnosis of the acute leukemias which is so difficult by the usual staining methods. The intensity of the reaction varies directly with the stage of maturity of the cells, being weakest in the myeloblasts and strongest in the polymorphonuclears. One observer[15] suggests that granules of oxidase ferment may not be demonstrable in very young myeloblasts. The eosinophile cells both in blood and tissues show the most active oxidases.

Owing to technical difficulties the indophenol-blue reaction falls somewhat short of the promise it gives at first thought, and modifications devised to obviate these difficulties are not trustworthy. But the methods outlined above, if followed in detail, afford a reaction on tissue sections that is of some value, and one on blood smears, that by reason of the ready differentiation between cells of lymphoid and myeloid origin made possible, is of real diagnostic importance.

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Discussion:

DR. LAMBERT: In two cases of myeloblastic leukemia recently observed in the Presbyterian Hospital, this reaction proved very valuable. Under casual examination I am certain that the cells in the blood would have been called lymphocytes. In fact, this mistake was made. The oxidase test proved conclusively, however, that the cells were of myeloid origin.

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CONTENTS

DEMONSTRATION OF THREE CASES OF SPLENIC ENLARGEMENT

MORTIMER WARREN, M.D.

These three specimens represent different types of splenic enlargement, and are presented to bring up the question of clinical differentiation, and pathological classification of splenomegalia in general, with reference to therapeutic splenectomy.

CASE I.—The spleen is from a patient presenting a well-characterized clinical condition with striking differential diagnostic signs, namely constitutional hæmolytic icterus. This spleen was removed by Dr. Charles H. Peck in May, 1912. A complete symptomatic cure resulted, namely relief of jaundice, and a reversal of a previously highly decreased osmotic tension of the red blood cells to one within normal limits. Histologically it is typical of that condition. The spleen is suffused with blood; this blood is chiefly interstitial; there is little or no fibrosis; follicles are somewhat crowded out. In other words, it is a spodogenous spleen tumor very similar to that of pernicious anæmia.

CASE II.—The spleen represents a type which has many designations but which seems to belong to the Banti group. Though still "*sub judice*," as an entity, Banti's disease has a place in any discussion of splenic enlargement. There is a group of cases in which clinical results are obtained by splenectomy which cannot be listed elsewhere except under the general terminology of "splenic anæmia." This spleen shows marked diffuse fibrosis without a great deal of capsular thickening, obliteration of follicles, and thickening of arterioles. There is little blood or congestion. (A small piece of liver removed at the time of the operation appears normal on section.) Splenectomy was performed by Dr. Charles H. Peck, March, 1914. The man was in good condition when last heard from, within a few months of the present time.

CASE III.—The patient showed an enlarged liver and spleen, jaundice, urobilin and bilirubin in urine, and clay-colored stools. There was nothing important in the blood findings aside from the auto-agglutinating property of the blood serum for the red blood cells (brought out only in the cold). Splenectomy was done by Dr. Charles H. Peck, September 15, 1915. Results so far are indefinite. The spleen shows wide open sinuses, areas of distended capillaries, abundant follicles, fibrosis of a fairly young character (cellular). The spleen looks as if it were in a hyperactive state, analogous to a lymph node in a state of irritative hyperplasia. A small bit of liver removed at the time of operation showed inflammation of a subacute character. There are periportal and scattered areas of round cell and polynuclear infiltration with some peri-portal increase of connective tissue. A diagnosis of peri-portal pylephlebitis was made.

I should like a discussion, especially in regard to the condition of the spleen accompanying cirrhosis of the liver, the spleen of malaria, and of syphilis.

Discussion:

DR. NORRIS: These cases are of great interest. Much importance has been attached to the spleen in regard to its association with various diseases. I do not feel able to give a competent opinion upon the lesions of the spleen. It has always been a subject of great dispute among pathologists. Even the

histology of the spleen has not been definitely settled. The lesions that Banti has described as characteristic for the disease known by his name, namely, fibro-adenia, I have found frequently present in the spleen where Banti's disease has not been present, namely, in association with many of the conditions found in middle life and also with recessive status lymphaticus. It is quite frequent to find thickened or nearly obliterated arteries of the splenic follicles, and often there are marked fibrous changes not only about the vessels but in the stroma. I cannot say, therefore, that these changes are characteristic of any one disease and therefore not characteristic of Banti's disease. A number of pathologists have described the spleen as presenting characteristic appearances not only in the gross but on microscopic section; this has not been my experience. In syphilitic cirrhosis of the liver, the enlargement of the liver is often marked and it is well known that the size of the spleen apparently bears no especial relation to the degree of the cirrhosis of the liver.

DR. LARKIN: We are in a hopeless condition, it seems to me, in regard to the classification of splenic lesions. I feel Dr. Norris is right. There are so many allied conditions which bring enlargement of the spleen which have no special characteristics, that we are hopelessly involved. Dr. Warren's specimen shows well marked enlargement and engorgement of the spleen in the thrombosis of the splenic vein. We do not know any more than we did many years ago about the exact condition of the circulation of the spleen, histologically.

DR. LEVY: What was the red cell count in these cases?

DR. WARREN: None of the three cases showed any anemia of any account.

DR. LEVY: Was there polycythemia?

DR. WARREN: No.

DR. ZINSSER: Did I understand Dr. Warren to say that one of these cases had hæmolysins for its own cells?

DR. WARREN: There were auto-agglutinins in the third case brought out only in the cold.

DR. ZINSSER: These conditions seem to be analogous to paroxysmal hæmoglobinuria.

DR. WARREN: I don't know what it means. There did not seem to be direct clinical indication for operation, except on the basis that the spleen had an important bearing on the liver condition and might keep up the disturbance in the liver.

DR. ZINSSER: In paroxysmal hæmoglobinuria an autolysin is found which does not act under the ordinary conditions of incubation. Hæmolysis occurs only when the sensitization has occurred at a low temperature and the tubes are consequently warmed up. I should like to ask whether there are any described splenic conditions associated with paroxysmal hæmoglobinuria.

DR. WARREN: I don't know. In these jaundice cases it is associated with the bile production.

WASSERMANN FINDINGS IN LOBAR PNEUMONIA

J. J. HERTZ, M.D.

My communication this evening is a preliminary report on the Wassermann findings in lobar pneumonia. At the Beth Israel Hospital where we do a Wassermann reaction on every patient admitted we found in a series of twelve cases the following results:

I. Ten of the twelve cases got well.

II. Every one of the ten cases that got well gave a "four plus" Wassermann reaction during the course of the disease, between the fifth and eighth day, and a negative reaction after the temperature became normal.

III. Of the two cases that died, one gave a "four plus" reaction on the sixth day and died on the seventh day. On autopsy the organs showed signs of syphilis. The other case that died gave a negative reaction on the eighth day about two hours before death. The only negative case died.

We are carrying on some experiments to find the nature of the substance that gives the reaction in these cases.

We used the original Wassermann test with the exception of the antigen which was an alcoholic extract of guinea pig's heart.

TRANSPLANTABLE SARCOMATA OF THE RAT LIVER ARISING IN THE WALLS OF PARASITIC CYSTS[1]

G. L. ROHDENBURG, M.D., AND F. D. BULLOCK, M.D.

(From Columbia University, George Crocker Special Research Fund, F. C. Wood, Director)

Primary sarcomata of the liver, while not common in man, are relatively frequent in rats, probably because of the relation

[1] This report appears in full in *The Journal of Cancer Research*, 1916, I, 87.

they bear to infection with the *Tænia crassicola.* In a series of autopsies on rats performed during the past three years, we have encountered three such tumors, two of which were recognizable in the gross, while one was of microscopic size only.

The first case has already been reported.[2] The second case occurred in a full-grown male, the tumor being situated in the left lobe of the liver and measuring one centimeter in diameter; metastases were scattered throughout the peritoneal cavity. The neoplasm, a spindle-cell sarcoma, is transplantable, and is now in the tenth generation, with an inoculation percentage of 100. About eighty per cent. of the takes retrogress spontaneously. Attempts to propagate the tumor by using a Berkefeld filtrate and dried tumor tissue were not successful. The third case occurred in an adult female; the tumor was situated in the Spigelian lobe and measured 1.5 cm. in diameter, and there were peritoneal metastases. This tumor also is transplantable, though the percentage of takes is not as high as in the case of the second tumor.

The chief point of interest in these cases is the demonstration of the parasite in the centers of the tumors.

Discussion:

DR. ZINSSER: I would like to ask whether it was at all possible to see where the tumor started.

DR. ROHDENBURG: The tumors started in the cyst wall surrounding the parasite.

DR. ZINSSER: Does the cyst wall originate from the capsule of the liver? Can the cysts be experimentally produced in rats?

DR. ROHDENBURG: Yes, the rats can be infected with the tenia and cysts produced in this way.

DR. NORRIS: Was the pancreas tumor an original tumor or a transplant?

DR. ROHDENBURG: It was a metastasis of the original tumor in the pancreas.

DR. ZINSSER: Is the percentage of tenia findings in rats very high; that is, is the percentage of tumors large or small as compared with the percentage of tenia infection?

DR. ROHDENBURG: The presence of the tenia in rats depends chiefly upon the condition in which the dealer keeps his animals. If he changes the drinking water frequently tenia infection is rare; if not, it is common. The tumors occur in only a small percentage of the infected animals.

DR. NORRIS: I would like to ask exactly what the sarcomatous process

[2] *Jour. Med. Research,* 1913, XXVIII, 477.

was in the transplants; in other words, what method of injection was used in the transplants.

DR. ROHDENBURG: The material used in the first case was the healthy part of the tumor, about 0.5 cm. distant from the parasite. In the second case, the metastases were used for transplantation.

DR. ZINSSER: You never had metastases in the experimental tumors?

DR. ROHDENBURG: No, not in the transplants.

DR. NORRIS: In other words, it is doubtful whether we can call the original tumors sarcomata?

DR. ROHDENBURG: If a malignant tumor can be defined as a collection of cells showing unlimited powers of division, I do not see why the primary tumors should not be called sarcomata. Even the fact that some of the transplanted tumors receded is not an argument against their sarcomatous nature. The Jensen sarcoma recedes in thirty out of fifty transplants; but some of the transplants grow, and produce metastases.

A CASE OF PORTAL THROMBOSIS WITH UNUSUAL COMPLICATIONS

JOHN H. LARKIN, M.D.

Thrombosis of the portal vein is not an unusually rare condition. This will be seen after a perusal of Lissauer's report in *Virchow's Arch.*, 1908, CXCII, 278, which states that among 26,687 cases coming to autopsy a condition of complete or partial occlusion of the portal vein was found sixty-eight times. His very interesting resumé also gives us an idea of the duration of such thrombi in the portal vein and its tributaries, together with the concomitant lesions, such as circulatory ileus, apparent in the most advanced cases. Numerous writers have contributed largely to the pathology of this condition, among whom we might mention Welsh, Versé, Rosenau, Pick, Heller, Lewis, Flexner, Whipple, Winternitz, Kohler, and Chiari. It is now well known that there is a close etiological relationship between portal thrombosis and bacterial infection, and this has been especially dwelt on by Welsh. The primary changes in the intima of the portal vein, together with a slowing of the blood stream, as well as compression of the vein by thickening of its adventitia, pressure of large lymph nodules in the vicinity of the hylus of the liver, or inflam-

matory adhesions to the wall of the vein are etiological factors which have been well pointed out by many observers. Its relationship with metastasizing tumor, either in the liver itself or in distant parts, blocking the vein with such growth, either directly or by extension into the vein itself, has not been so often referred to in the literature of this condition.

It is interesting to note that in all the cases of portal thrombosis which have been reported the liver itself suffers very little secondarily from such circulatory disturbances as would lead on to infarction.

I wish, however, to present a condition of thrombosis, the etiology of which is foreign to our ordinary conception of the disease. It presents a number of factors of great clinical significance, and on account of the close clinical picture of the individual during life with that of cirrhosis of the liver, I trust that the presentation will be of interest to all.

The history of the individual is as follows:

A negro; forty-five years of age; admitted to City Hospital on February 17, 1915. Died March 30, 1915. Chief complaint was swelling of legs and shortness of breath. Family history: Father died at eighty years, of senility; mother died at sixty-four, cause unknown. Patient was one of fifteen or sixteen children, some of which died in infancy, but the majority are living and well. There was no tuberculosis, cancer, alcoholism, heart, kidney, or venereal disease elicited in the family history. Personal history: Had the ordinary diseases of childhood: measles, diphtheria, typhoid fever, etc. No history of venereal disease obtainable. Occupation was that of a private chef in one of the clubs, where he had been employed for a number of years; he was a mild drinker of beer and whiskey. Three and one half or four years ago patient had an axillary abscess, which was opened.

Last July, while in apparently the best of health, in helping remove a trunk he was thrown down a flight of stairs, a distance of some twenty feet, striking on the trunk at a point on his abdomen midway between the ensiform and the umbilicus in the median line. Upon being picked up and examined it was found that a small hematoma had developed in the rectus muscle, about

five cm. below the ensiform. This hematoma was from five to six cm. in diameter. It was not accompanied by any unusual pain at the time, except for skin tension. He was advised by his physician to go home. Late on the same evening, around nine o'clock, he commenced to complain of lancinating, shooting pains in his abdomen, accompanied by a partial collapse and vomiting, the vomitus being a yellow, bile-colored fluid. The pain at this time became so severe that opiates had to be administered. On the following day the patient was no better. He remained in bed for a period of two weeks, during which time the pain had diminished in severity, being deep-seated in character.

In the beginning of August the patient's legs became quite markedly swollen, and in one of his attacks of vomiting he had a hematemesis of bright red blood, jelly-like in consistence and about four ounces in quantity. He was treated by his physician for gastric ulcer.

About the beginning of October his abdomen commenced to swell, but not to such an extent as to make him feel uncomfortable. Swelling of the legs continued and shortness of breath was marked at this time. Examination of his abdomen gave fluid wave by percussion. Patient seemed rather anxious in his manner, and commenced to be emaciated. His color was a light yellowish, which was most marked in the conjunctivæ.

About November 1, patient had a very large gastric hematemesis, losing about a quart of clotted, jelly-colored blood, and at about this time it was noted that his stools were dark and tarry-colored, evidently occult blood. From this time on the patient seemed to become more and more depressed. The swelling of the abdomen became larger and larger, and by the first of December fluid had accumulated to such an extent that it was deemed necessary to tap the patient in order to relieve the fullness of his abdomen. A very large quantity of straw-colored fluid was obtained at this time, after which the patient went into a collapse. Soon after another large hematemesis occurred, which contained many jelly-like clots. The patient's condition at this time was that of a fretful and worried individual. The deep-seated pain now seemed to have disappeared.

The patient remained quietly at home until the first part of February, when he was removed to the City Hospital. Upon admission the patient was found to be a fairly well nourished individual. His abdomen was swollen and both legs were moderately edematous. He complained of a dull, deep-seated pain in his abdomen; his expression was anxious, and he was short of breath. The anemia of the individual was well marked, denoting great loss of blood. On the day of his admission, Feb. 17, patient had another large gastric hematemesis. His stools were tarry-black in color. From this time on until March 30, the patient remained in bed, complaining little, except of abdominal pains and shortness of breath; also of an increasing distress on account of abdominal fluid. On March 10, patient complained so much that tapping was resorted to, and a large amount of straw-colored fluid was withdrawn. On March 27, patient had another large gastric hematemesis, which was repeated on the following day. On March 29, the patient was found in a very weak condition; the abdomen was again commencing to distend. On March 30, patient refused nourishment. He had a final hemorrhage of a large amount of blood containing many clots, and died shortly afterwards. An autopsy was performed on the following day.

The autopsy findings were as follows: Body is that of a fairly well developed colored man about forty-five years of age. There are no physical abnormalities upon external examination.

Heart weighs 500 gm. The left ventricle is dilated. Muscle is pale, friable and flabby. Width of the aorta about the aortic valve is 7 cm. Depth of ventricle is 7 cm. Thickness of the wall of left ventricle is 1.5 cm. While the aorta is slightly thickened, its intimal surface is smooth, except for several slightly raised nodulations, mostly of a fatty atheroma. The pulmonary orifice measures 9 cm. Tricuspid valve measures 13 cm. Mitral valve measures 9 cm. Foramen ovale is closed. Aortic valves are competent; they are slightly thickened along their free edges. The mitral, tricuspid and pulmonary valves show no lesions.

Left lung weighs 500 gm. Organ is bound down in the pleural cavity by adhesions. It is voluminous; contains about the normal amount of pigment. Mucous membrane of the bron-

chus is pale; there is no thrombus in the pulmonary artery or veins. The lung is air-containing throughout. On section the posterior and dependent part shows edema and a moderate congestion. There is no pneumonia. On section upper anterior lobe is pale and anæmic. There is no edema.

Right lung weighs 600 gm. It is bound down in the cavity by adhesions. Lower base of right lung shows compression atelectasis by fluid in the pleural cavity.

Liver weighs 1,600 gm. Portal vein is thrombosed. Surface of organ is indented and irregular. Consistence of organ is firm. Surface is indented by deep cicatricial scars, bringing about a great deformity of the liver. There is atrophy of the extreme left lobe of liver. The capsule is thickened by an irregular veil-like thickening, which evidently is a distension of the lymphatics. On section, liver shows a rather uniform appearance. Markings are partly obliterated. There is no evidence of connective tissue. The thrombus extends even into the portal radicles. The gall-bladder is enormously distended with bile; no stones.

Spleen weighs 800 gm. Organ shows a chronic interstitial splenitis. Splenic vein at its middle and distal portion is extremely dilated, and at about the junction of the inferior mesentery and the splenic vein there is an aneurismal dilatation at that point in the vein in which there is a parietal, organized thrombus. This has extended up into the portal vein, completely occluding its lumen. It is glistening-white in color, and shows partial canalization.

Pancreas shows extreme atrophy, the normal pancreatic tissue being replaced by fat. There is a supernumerary pancreas.

Left kidney weighs 350 gm. It measures $11 \times 6 \times 3.5$ cm. It is uniformly glazed, and has the appearance of amyloid. The organ does not, however, react to iodin. Markings are obliterated; organ is elastic; has an almost stony hardness; it is not congested. The Malpighian bodies are slightly seen. Capsule of kidney is not adherent, but when pulled off diffuse cicatricial wedges of fibrous connective tissue can be seen. Organ has the appearance of a subacute diffuse nephritis.

Right kidney weighs 325 gm. It measures $11 \times 6 \times 3.5$ cm.

Organ is enlarged; capsule strips with ease. On section it is similar to the left, except that it is slightly more reddish in color. The surface beneath the capsule is not granular. The markings of the kidney are obliterated.

Aorta is slightly thickened; its elasticity is slightly diminished; there is a moderate atherosclerosis, but fatty change in the intima is the most pronounced change. There is no calcification; no evidence of syphilitic atheroma.

Bladder is distended with urine; mucous membrane appears pale, but is normal.

Small intestines are full of blood, which has recently stained the mucosa.

Stomach is dilated and full of blood. It shows a hypertrophic gastritis.

Esophagus is unusually dilated. The venous radicles are enormously distended, and at a point 4 cm. above the pyloric end of the stomach there is an ulcerated area in the mucous membrane leading directly into the esophageal plexus, from which constant bleeding has occurred. Above, at a distance of 13 cm., are three other ulcerated areas, the largest of which is 1 mm.

Anatomical diagnosis: Thrombosis of the portal vein, extending into the portal tributaries and liver; varicosities of the esophageal vein (extreme); multiple rupture of varices; acute diffuse nephritis; chronic hyperplastic spleen; atheroma of aorta; supernumerary pancreas in the duodenum; degeneration of the myocardium; fatty infiltration of pancreas.

Upon further examination of the esophagus, four longitudinal, greatly distended varices take up the lower third of the esophagus; the largest of these measures 2 cm. in diameter. The varices are of unusual dimensions, and many punctate points, filled with thrombi, can be seen.

I thought on account of the enormity and intense dilatation of the varices that it would be a good opportunity for the study of such varices. I therefore placed a cannula in one of the lower varices and washed out with cold water the whole esophageal venous system. I then made a mixture of red oxide of lead and chalk (a mixture which is commonly used in making arterial

injections in the autopsy room) and using only slight pressure, filled the esophageal varices, the fluid entering with little or no difficulty. After dissecting out the esophagus, it was placed in cold water until the following day, when an *x*-ray of the distended varices was taken, an illustration (Fig. 1) of which is herewith reproduced.

In a resumé of the literature on thrombosis of the portal vein we find that it is not unusual for this condition to be accompanied by esophageal varices, and that one of the attending clinical features is gastric hematemesis. But in a very careful examination of the literature of such cases no report of a case of portal thrombosis is disclosed which shows so enormous a distention of the esophageal varices or an illness which existed for so long a time as the case which I present to you here to-night. The only case approaching it in this respect was the one reported by Versé, and this, it should be remembered, was some ten years ago. His case is rather unique, and corresponds fairly well with the case presented to you now. Versé, however, gave no measurements of the esophageal distention, nor did he give measurements of the esophageal varices.

I think I am safe in stating that never before has a similar specimen been presented to this Society prepared as this specimen has been prepared, presenting, as it does, a clean-cut anatomical view of the esophageal varices, and showing to what a huge extent such varices may be distended.

The transverse measurement of the esophagus taken at the time of autopsy is 12 cm., and the largest varix, which is almost a venous aneurism, measures 2 cm.

Many punctate points may be seen, from which bleeding has occurred from the distended veins.

A further dissection of the organs reveals the following:

The spleen is enormously enlarged, and on section of the pancreas from tail to head one immediately encounters the distended splenic vein, which, at its middle part, measures 1.5 cm. Just before the splenic vein meets to form the portal there is a giving way of the splenic vein, and an aneurism has formed, the wall of which is now lined by a laminated and organized clot, pearly-white in color, and of firm consistence. From this point on the portal vein is entirely thrombosed, reaching up to the portal radicles. Yet upon macroscopical examination the liver is found to be negative, except that the superior surface of the left lobe seems to be indented by deep cicatricial scars, the apex of which was toward the greater bulk of the liver substance, and

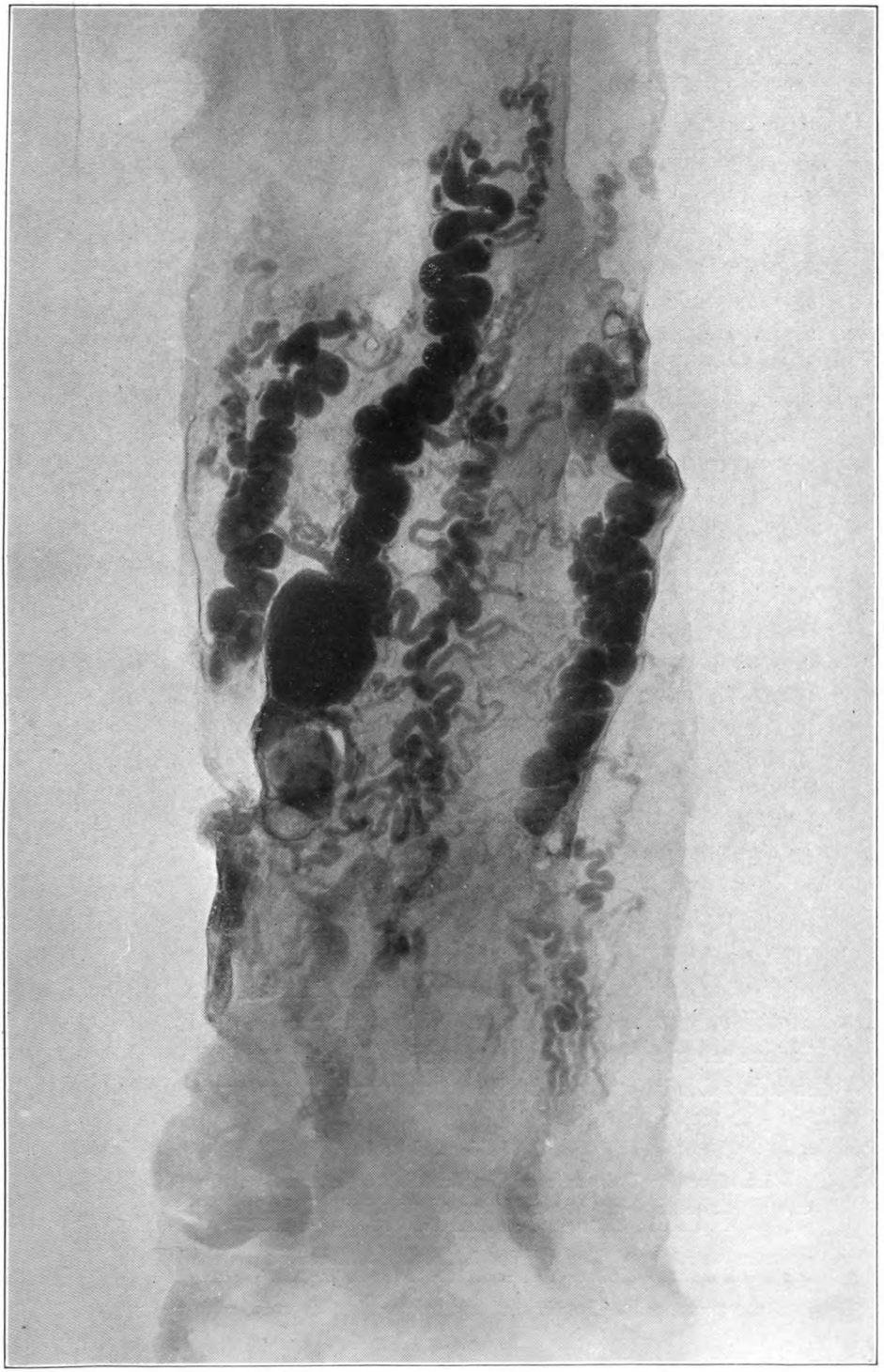

FIG. 1. Excessive Esophageal Varix in a Case of Portal Thrombosis.

the base peripherally pulling down and deforming the greater part of the liver tissue. Some of these cicatrices measure 1 cm. from base to apex.

Microscopical examination of the splenic aneurism and portal vein shows a trauma, with resulting aneurismal dilatation in the splenic vein at its junction with the portal. Here the thrombus at its peripheral part is organized, the wall of the vein having given away and showing a much older pigment distributed throughout in the neighborhood of the pancreatic tissue. Examination of the portal vein shows beginning parietal organization, the central part, however, being composed of a firm mixed clot.

Microscopical examination of the liver shows no pathological changes. The cicatrices at the peripheral part of the liver capsule show large triangular areas of dense fibrous connective tissue, in which the hepatic artery and the portal radicles seem to be condensed by such fibroses. No infarction of the liver can be made out either macroscopically or microscopically, and the present interpretation of such cicatricial wedges does not now seem clear to the writer.

This case is of unusual interest, not only to the clinician but to the pathologist, by reason of the very close clinical picture exhibited in portal thrombosis, and disturbances of the portal circulation in cases of cirrhosis of the liver.

It is of far greater interest, however, on account of the etiological factor presented, which is undoubtedly one of trauma—a factor which has not heretofore been mentioned in any report of similar cases. It presents great clinical interest, too, by reason of the enormous distention to which the esophagus may be put before rupture and death intervene. The extent of this dilatation is faithfully shown in the accompanying photograph (Fig. 1).

Discussion:

DR. NORRIS: This case of Dr. Larkin's is interesting. In the photomicrograph shown there was evidence of phlebitis. I don't think there is any doubt that trauma was the etiological factor in this case. I notice that the pancreas was large. The relation between latent and sub-latent infections of the pancreas and appendix is interesting. The veins of these organs drain into the portal vein. In view of the trauma in this case, with the damaged

vein, there probably developed a lesion of the portal vein which gave rise to thrombosis. In regard to the esophageal dilatation, the thrombus must have been acute and the veins were not able to take care of the distention.

DR. LARKIN: I am glad to hear Dr. Norris has agreed with me in the view of trauma as an etiological factor. I have looked over this subject very thoroughly. In all the cases that have come under my observation the question of trauma has never arisen. I have asked a number of well-informed clinicians but have had no agreement on the etiology of this condition.

BILATERAL INFARCTION OF THE SUPRARENAL BODIES

JOHN H. LARKIN, M.D.

The specimen of infarction of the suprarenal bodies presented to you this evening is so very rare that it deserves more than passing notice. There has been no case similar to it reported in medical literature, save a meager resumé of a unilateral thrombosis of the suprarenal, described by Paul G. Woolley in the *Journal of Medical Research,* 1902. That was a case of an eleven-months-old child, in whom he had found a thrombus of the right adrenal vein, with resulting engorgement and infarction. It is quite well known that hemorrhages in the suprarenal bodies may be unilateral or bilateral, and may be found at the time of autopsy in newborn infants, but to this I do not refer.

The history of the case presented here tonight, in keeping with the findings, is very unusual.

The patient was a young man twenty-four years of age, a muscular iron-worker. He had worked until his admission to the City Hospital on June 16, 1915. His first symptoms were those of pain in the abdomen, in the region of the ensiform. The pain was of a lancinating character, so that opiates had to be administered to control it. The patient's personal and family history were both negative. He was married, and had one child; he denied the use of alcohol and tobacco. A Wassermann test made at time of admission gave a negative result. Temperature upon admission was 101°. A blood culture taken the same day gave negative findings. Patient was hard to control; he wanted

to wander around the ward; at times he was doubled up with pains in the abdomen, crying that something be done for his relief. Up to this time no definite diagnosis had been made.

On June 20 patient's pains were slightly decreased; had one vomiting spell; lay rather quietly in bed under opiates.

On June 23 the patient's temperature was 103°, and his abdomen was now tympanitic. Blood cultures taken on June 22 and 23 proved negative.

On June 24 the patient was depressed and had the facial expression of one suffering; the knees were flexed; patient was evidently in a septic condition.

On June 25 blood culture was still negative.

On June 26 patient went into collapse. His abdomen was now distended with gas, and a provisional diagnosis of peritonitis was made.

On June 27 patient went into coma, and died soon after. No surgical operation was made in this particular case.

An autopsy on June 27 revealed the following:

Body is that of a well-nourished and well-developed young man. Rigor mortis is still present; lividity is present on the posterior and dependent portions of body. There are no external physical abnormalities or scars found. Upon opening the abdominal cavity free gas escapes, and the cavity is found filled with fluid pus, yellowish in color. There is about 4.5 liters of this pus. The greater omentum is necrotic, and occupies the epigastric region. The serosa of the intestines is covered with a flocculent, fibrinous exudate. The intestines are adherent to each other. The proximal portion of the appendix is inflamed, and the gland appears necrotic. Upon removing the large and small intestines and separating the adhesions we find in the epigastric region a ruptured ulcer. This ulcer extends to the duodenum, just beyond the pyloric end of the stomach. The thoracic cavity is free of fluid. Base of left lung is adherent to the diaphragm. There is an acute fibrinous pleurisy at base of right lung, which is slightly adherent to the diaphragm.

Heart weighs 290 gm. Pericardial sac contains about 20 cc. of straw-colored fluid. Right side of heart is filled with a

chicken-fat clot. Foramen ovale is closed. Mitral measures 9 cm. Mitral valve is normal. Tricuspid valve measures 12 cm. It is likewise normal. Pulmonary valve measures 6.5 cm. There is a slight atheroma just above this valve. The heart muscle on section is beefy-red, firm in consistency, but shows no gross change. The coronaries are normal.

Left lung weighs 550 gm. Pleura is everywhere smooth, except at base, where it is roughened and hemorrhagic. Bronchus is injected, and covered with a serous exudate. Pulmonary vessels are normal. On section lung shows only congestion.

Right lung weighs 600 gm. Externally it is similar to the left. Bronchus of this lung is likewise injected. On section the organ shows only congestion and a moderate amount of edema.

Aorta is normal.

Bladder is normal.

Ureters are normal.

Liver weighs 2,150 gm. On section lobules are indistinct. Liver is the seat of a diffuse parenchymatous degeneration. Gall-bladder contains no stones.

Spleen weighs 250 gm. Capsule is thickened, and covered with an organized fibrin. On section organ shows sepsis. The Malpighian bodies are not as distinct as normally.

Left kidney weighs 300 gm. On section organ is the seat of an acute parenchymatous degeneration.

Left adrenal measures 3 x 4 cm. On section it is a deep black in color; consistence is firm, and it is with difficulty that one can distinguish the medullary from the cortical area.

Right kidney weighs 300 gm. On section this organ is similar to the left.

Right adrenal is the seat of a diffuse hemorrhage. Its measurements are the same as the left. On section it presents a condition perfectly similar to the left, the gland being a deep black in color; dry, and on section it is impossible to tell the difference between the cortical and medullary zones. On dissection of the left adrenal vein the lumen is blocked with a mixed white and red thrombus, completely distending its lumen, and stopping rather short in a "finger-gloved" appearance at its entry into the renal

vein. A similar thrombus is found in the right adrenal vein, which completely blocks the lumen. This thrombus is firm, red and white in color, and likewise stops short at its entry into the inferior vena cava.

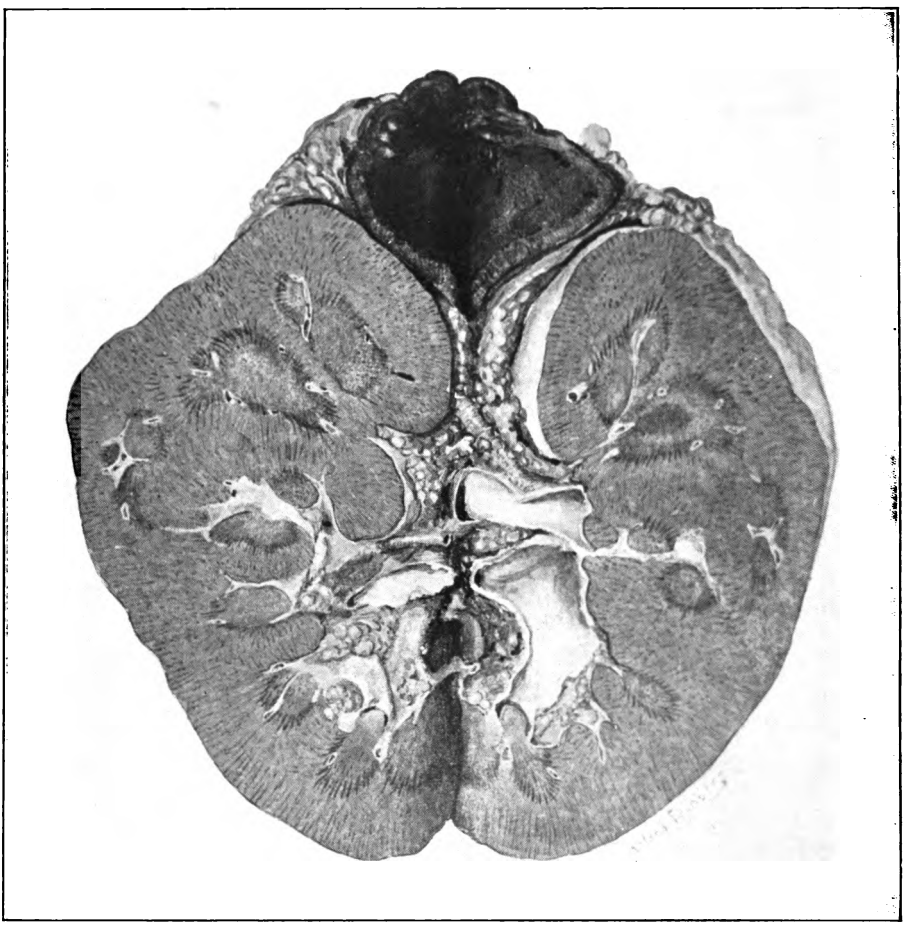

FIG. 2. Hemorrhagic Infarction of Suprarenal in a Case of Perforating Duodenal Ulcer.

Duodenum shows an ulcer about 5 cm. in diameter, which has ruptured into the abdominal cavity.

Anatomical Diagnosis: Bilateral fibrinous pleurisy at bases of lungs; congestion of lungs; septic spleen; cloudy swelling of liver; acute parenchymatous degeneration of kidneys; generalized acute purulent peritonitis, following a rupture of duodenal ulcer; bilateral infarction of adrenals.

This case is one of unusual interest and of great pathological rarity, and only a brief resumé of the condition is presented at this time. It may be well to note that all the writers on thrombosis have failed to describe a condition similar to the one which is presented here in this case. Not even Welsh in his memorable lectures on embolism and thrombosis mentions it, and a close review of the Goulstonian lectures on the suprarenal bodies by Rolleston fails to reveal any mention of this lesion.

The intensity of the infarction is similar in color and consistence to those infarctions that we find in the lung.

The intensity of the infarction is great (Fig. 2) and it may be well to repeat here what Welsh says in his lectures on embolism and thrombosis: "That if the veins are obstructed sufficiently to render the outflow nothing, or exceedingly small, and if the arteries are at the same time open, the infarction is intense."

It is exceedingly difficult to trace the origin of the thrombus in both adrenal veins. Undoubtedly its occurrence in a case of septic peritonitis following a duodenal ulcer which had perforated is a factor. Indeed, one might say that in origin it was probably of bacterial marantic thrombus.

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